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Nursing Home Admission and Initiation of Domiciliary Care After Ischemic Stroke − The Importance of Time to Thrombolysis

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Objectives: There is a paucity of data on the risk of nursing home admission or domiciliary care initiation according to time to intravenous thrombolysis for ischemic stroke. We investigated the association between time to intravenous thrombolysis and the composite of nursing home admission or domiciliary care initiation in patients with acute ischemic stroke. *Materials and Methods:* In this nationwide cohort study, all stroke patients treated with intravenous thrombolysis (2011−2015) and alive at discharge were identified from the Danish Stroke Registry and other nationwide registries. The composite of nursing home admission or domiciliary care initiation one year post-discharge according to time to thrombolysis was examined with multivariable Cox regression. *Results:* The study population comprised 4,349 patients (median age 67 years [25th-75th percentile 57−75], 65.2% men). The median National Institutes of Health Stroke Scale score at presentation was 5, and the median time from symptom-onset to initiation of thrombolysis was 143 min. The absolute 1-year risk of the composite endpoint was 14.0% (95%CI, 11.5−16.8%) in the ≤90 min group, 16.6% (15.1−18.1%) in the 91−180min group, and 16.0% (14.0−18.2%) in the 181−270 min group. Compared with thrombolysis ≤90 min, time to thrombolysis between 91−180 min and 181−270 min was associated with a significantly higher risk of the composite endpoint (hazard ratio 1.31 [1.04−1.65] and 1.47 [1.14−1.91], respectively). *Conclusions:* In patients admitted with ischemic stroke, increasing time to thrombolysis was associated with a greater risk of the composite of nursing home admission or domiciliary care initiation. Continued efforts to shorten the time delay from symptom-onset to initiation of thrombolysis are warranted.

Key Words: Stroke—Thrombolytic therapy—Nursing home—Epidemiology

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Introduction

Stroke is a leading cause of death and acquired disability worldwide.[1,2] In patients with acute ischemic stroke, thrombolytic therapy with intravenous recombinant tissue-type plasminogen activator within 270min after symptom-onset is a medical treatment known to improve outcomes.[3–6] It is well-established that treatment delay decreases the beneficial effect of thrombolytic therapy and consequently, international guidelines for the management of acute ischemic stroke recommend this treatment to be initiated in eligible patients without any delay.[3–8] However, these recommendations are derived from data from older studies, and outcome assessment has primarily focused on traditional clinical outcomes such as mortality, degree of disability, and functional independence. The need for professional assistance to carry out daily life activities at home, such as domiciliary care, or at institutions, such as a nursing home, represents another metric of quality of care. The need for domiciliary support or admission to a nursing home not only represents a substantial economic burden on society, but also carries significant personal implications for the individual, including loss of independence and self-esteem, loneliness, and potentially depression and other mental health problems.[9,10] However, there is a paucity of data on the risk of nursing home admission and domiciliary care initiation according to time to thrombolytic therapy. Evaluation of such outcomes may not only help to identify patients who are at high risk of poor outcomes, but also provide novel insights on the importance of time to initiation of intravenous thrombolytic therapy on post-discharge 1-year outcomes. Consequently, we examined the risk and factors associated with nursing home admission and domiciliary care initiation in a large nationwide cohort of patients with acute ischemic stroke according to time to thrombolysis.

Methods

The Danish healthcare and social welfare systems

The Danish healthcare system is tax-funded and provides free 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, disability pension, admission to nursing home, and domiciliary care.

Stroke management and the Danish Stroke Registry

Intravenous thrombolysis with recombinant tissue-type plasminogen activator became a nationwide treatment in Denmark in 2008.[11] In Denmark, thrombolysis is administered by neurologists at dedicated regional primary stroke centers with telemedicine treatment in associated satellite stroke units, with subsequent referral within 24 h 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.[12] 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 are >90% in the Danish Stroke Registry.[13] The database 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, brain imaging, and treatment.[12]

Other data sources

All Danish citizens are assigned a unique and permanent civil registration number allowing an accurate linkage of nationwide administrative and clinical registries at an individual level. The Danish Stroke Registry was linked with the following nationwide administrative registries: 1) The Danish National Patient Registry; 2) The Danish National Prescription Registry; 3) The Danish Civil Registration System; and 4) Statistics Denmark. The Danish registries are validated, of high quality, and have been described in detail previously.[14–19]

Study population

All Danish citizens who were admitted with ischemic stroke and treated with intravenous thrombolytic therapy between January 1, 2011 and December 31, 2015 were identified through the Danish Stroke Registry. Patients were excluded if they were living in a nursing home or received domiciliary care prior to admission, or if they died during admission.

Study variables

Data on comorbidity were obtained using in-hospital and outpatient diagnosis codes any time prior to the discharge date (Table 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.[20] Concomitant pharmacotherapy was defined as claimed prescriptions within 180 days prior to admission (eTable 2 for Anatomical Therapeutic Chemical Classification System codes). 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

Table 1. *Baseline characteristics of the study population*

Characteristics	Time from symptom-onset to thrombolytic therapy				*p*-value
	≤90 min N = 577	91−180 min N = 2,043	181−270 min N = 953	> 270 min N = 146	
Demographics					
Age, median(25^{th}−75^{th} percentile)	67(58−74)	68(58−75)	67(57−75)	66(55−74)	0.09
Age, categorical					0.10
≤ 60 years	199(30.2)	704(29.4)	376(33.3)	59(34.7)	
61−70 years	222(33.7)	720(30.1)	339(30.0)	49(28.8)	
71−80 years	180(27.4)	706(29.5)	296(26.2)	41(24.1)	
≥ 81 years	57(8.7)	261(10.9)	119(10.5)	21(12.5)	
Male, N(%)	442(67.2)	1,553(65.0)	730(64.6)	120(70.6)	0.33
Income group, N(%)					0.001
Q1(lowest)	118(17.9)	519(21.7)	235(20.8)	21(12.4)	
Q2	125(19.0)	550(23.0)	253(22.4)	48(28.2)	
Q3	180(27.4)	661(27.7)	299(26.5)	47(27.6)	
Q4(highest)	235(35.7)	661(27.7)	343(30.3)	54(31.8)	
Marital status, N(%)					0.44
Living alone	174(26.4)	622(26.0)	323(28.6)	47(27.6)	
Prior history, N(%)					
Ischemic stroke	63(9.6)	274(11.5)	137(12.1)	15(8.8)	0.28
Ischemic heart disease	103(15.7)	463(19.4)	213(18.8)	21(12.4)	0.03
Heart failure	43(6.5)	149(6.2)	74(6.5)	10(5.9)	0.97
Atrial fibrillation	128(19.5)	406(17.0)	170(15.0)	39(22.9)	0.02
Hypertension	343(5.2)	1,319(55.2)	585(51.8)	93(54.7)	0.22
Diabetes	70(10.6)	248(10.4)	144(12.7)	20(11.8)	0.20
Peripheral artery disease	24(3.6)	114(4.8)	43(3.8)	4(2.4)	0.24
Malignancy	55(8.4)	259(10.8)	94(8.3)	9(5.3)	0.01
Chronic kidney disease	19(2.9)	85(3.6)	34(3.0)	9(5.3)	0.38
Chronic obstructive pulmonary disease	42(6.4)	144(6.0)	71(6.3)	9(5.3)	0.95
Liver disease	5(0.8)	32(1.3)	17(1.5)	< 3	0.46
Pharmacotherapy, N(%)					
Antiplatelets	272(41.3)	1,157(48.4)	526(46.5)	78(45.9)	0.02
Oral anticoagulants	51(7.8)	133(5.6)	63(5.6)	12(7.1)	0.16
Lipid-lowering drugs	296(45.0)	1,074(44.9)	480(42.5)	75(44.1)	0.57
NIHSS at presentation, median (25^{th}-75^{th} percentile)	6(3−12)	5(3−9)	5(3−8)	6(3−10)	< 0.001
NIHSS at presentation, N(%)					< 0.001
0-3	178(27.1)	707(29.6)	431(38.1)	52(30.6)	
4-5	112(17.0)	517(21.6)	238(21.1)	28(16.5)	
6-9	136(20.7)	549(23.0)	251(22.2)	42(24.7)	
10-43	216(32.8)	587(24.5)	197(17.4)	46(27.1)	
Missing	16(2.4)	31(1.3)	13(1.2)	< 3	
Endovascular therapy	114(17.3)	272(11.4)	83(7.3)	14(8.2)	< 0.001

according to quartiles. Time from symptom-onset to initiation of thrombolytic therapy was classified into the following clinically relevant categories: ≤90 min, 91−180 min, 181−270 min, and more than 270 min.[4]

Outcomes

The primary outcome was the composite of admission to a nursing home or initiation of domiciliary care. The primary composite outcome, which was predefined, was chosen as both components of the primary outcome represent the need for professional assistance to carry out daily life activities. However, as patients admitted to nursing homes have a greater and more comprehensive need of care, we also analyzed this outcome separately. In addition, we examined all-cause mortality. Patients were followed from the discharge date until the occurrence of an outcome of interest, death, emigration, or a maximum of 1 year of follow-up. By design, all patients had at least 1 year of potential follow-up.

A nursing home is defined as an institution where citizens live if they can no longer take care of themselves.[19] Domiciliary care is defined as help administered if there are assignments in the home that citizens can no longer do themselves. Domiciliary care in Denmark covers three main areas: 1) personal care, including bathing, dressing,

and eating; 2) practical help, including shopping, cleaning, and doing laundry; and 3) food service.[21]

Statistical analyses

Baseline characteristics were reported as frequencies with percentages or medians with 25th–75th percentiles. Differences in baseline characteristics according to time to thrombolytic therapy were tested with the Chi-square or Fisher's exact test for categorical variables and the Mann-Whitney test for continuous variables. The absolute risks of the composite of nursing home admission or domiciliary care initiation and nursing home admission according to groups were estimated using the Aalen-Johansen estimator, taking the competing risk of death into account, and differences were assessed using Gray's test. Survival curves according to groups were estimated with the Kaplan Meier estimator, and differences were assessed using the log-rank test. Cause-specific Cox regression models were used to examine the rates of outcomes according to time to thrombolytic therapy. Hazard ratios (HR) with 95% confidence intervals (CI) were estimated, adjusted for age (categorical variable: ≤60 years, 61–70 years, 71–80 years, ≥81 years), sex, income, status on living alone, comorbidities (listed in Table 1), stroke severity (categorical variable according to quartiles: i.e. NIHSS-score 0–3, 4-5, 6–9, 10–42), endovascular therapy, and year of stroke. Patients treated with thrombolytic therapy within 90 min after symptom-onset served as the reference group in all models. Interactions between treatment delay and clinically relevant variables (including age, sex, and stroke severity) on outcomes were tested for and found insignificant. The association between time to thrombolysis and the composite outcome was also evaluated using a restricted cubic spline regression model, adjusted for age, sex, stroke severity, and endovascular therapy. Knots were placed at the 5th, 35th, 65th, and 95th percentiles. 90 min from symptom-onset to initiation of thrombolysis was used as the reference. All statistical analyses were performed with SAS 9.4 and R version 3.6.1. 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, which was missing for 1.4% of patients. These patients were excluded from the Cox regression models.

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 Capital Region of Denmark (approval number: P-2019-523) in accordance with the General Data Protection Regulation and the Danish Clinical Quality Program – National Clinical Registries.

Results

From January 1, 2011 to December 31, 2015, 5,736 patients with acute ischemic stroke received intravenous thrombolytic therapy. After exclusion criteria were applied, 4,349 patients comprised the study population (Fig. 1). The median age of the study population was 67 years (25th–75th percentile 57–75 years), and 65.2% were men. The median NIHSS score at presentation was 5 (25th–75th percentile 3–9), and the median time from symptom-onset to initiation of intravenous thrombolytic therapy was 143 min (25th–75th percentile 107–194). In total, 483 (11.1%) patients underwent endovascular therapy. Baseline characteristics according to time to thrombolytic therapy are summarized in Table 1.

Nursing home admission or domiciliary care initiation

The absolute 1-year risk of the composite of nursing home admission or domiciliary care initiation overall was 16.1% (95% CI 15.0–17.2%). The absolute 1-year risk of the composite endpoint was 14.0% (11.5–16.8%) in the ≤90 min group, 16.6% (15.1–18.1%) in the 91–180 min group, 16.0% (14.0–18.2%) in the 181–270 min group, and 17.1% (11.8–23.1%) in the >270 min group (Fig. 2a). Time to thrombolytic therapy between 91–180 min and 181–270 min was associated with a significantly higher risk of the composite endpoint compared with

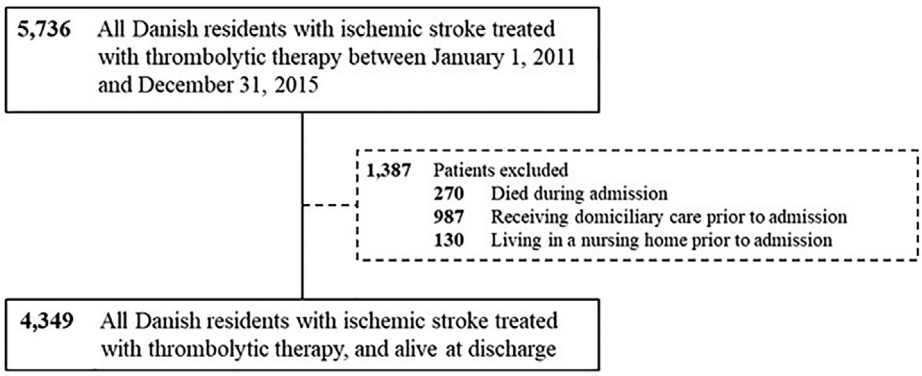

Fig. 1. *Flow chart of the study population selection process.*

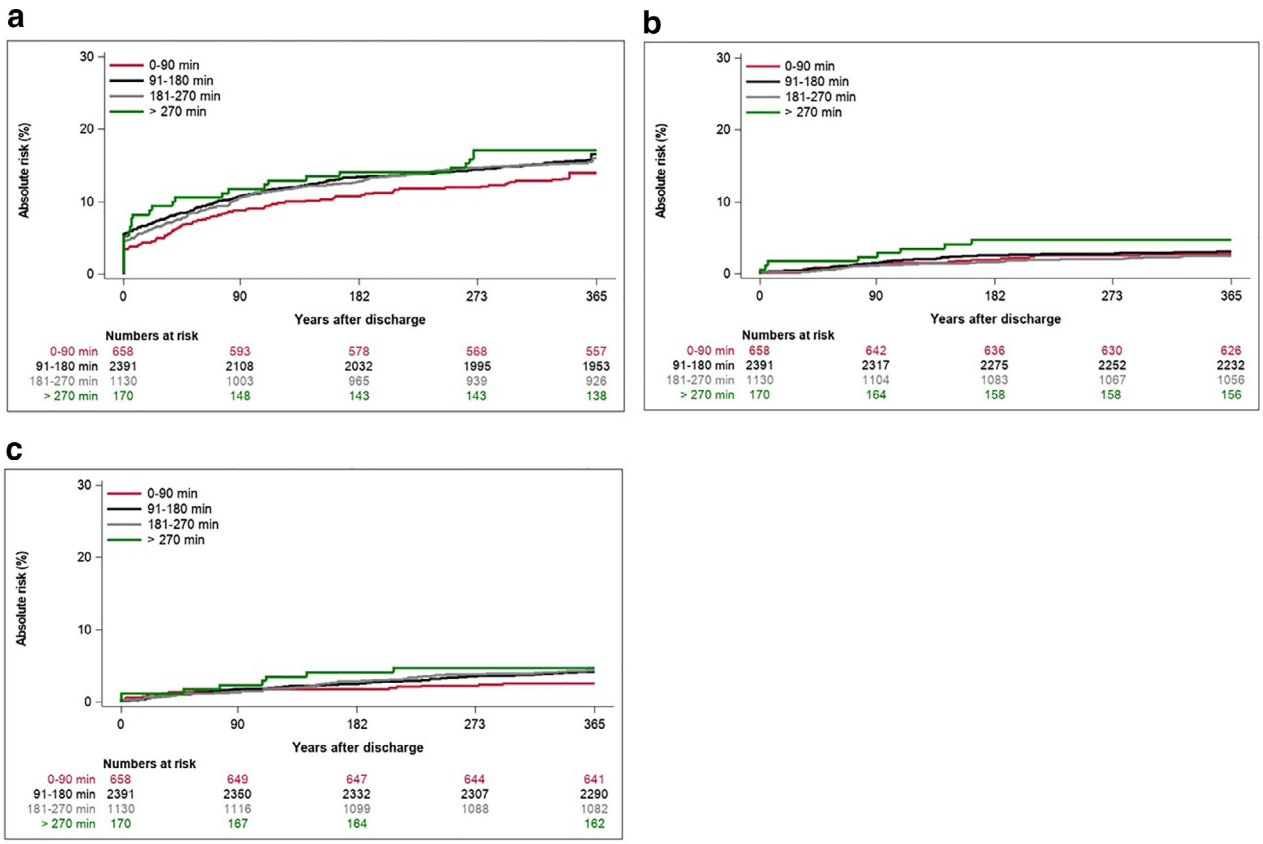

Fig. 2. *Absolute risks of outcomes. (a) Composite of nursing home admission or domiciliary care initiation. (b) Nursing home admission. (c) Death*

thrombolytic therapy received ≤90 min of symptom-onset (adjusted HR 1.31 [1.04−1.65] and 1.47 [1.14−1.91], respectively). Time to thrombolytic therapy >270 min was not associated a significantly higher risk of the composite endpoint compared with thrombolytic therapy received ≤90 min of symptom-onset (adjusted HR 1.29 [0.84−1.99]). There was no interaction between time to thrombolytic therapy and stroke severity on the risk of nursing home admission or domiciliary care initiation (*p*-value for interaction 0.83).

In the restricted cubic spline regression analysis, the risk of the composite outcome increased with increasing time to thrombolysis (Fig. 3).

Nursing home admission

The absolute 1-year risk of nursing home admission overall was 2.9% (2.5−3.5%). The absolute 1-year risk of nursing home admission was 2.7% (1.7−4.2%) in the ≤90 min group, 3.1% (2.5−3.9%) in the 91−180 min group, 2.5% (1.7−3.5%) in the 181−270 min group, and 4.7% (2.2−8.7%) in the >270 min group (Fig. 2b). In adjusted analysis, time to thrombolytic therapy between 91−180 min, 181−270 min, and >270 min was not associated a significantly higher risk of admission to a nursing home compared with thrombolytic therapy received ≤90min of symptom-onset (adjusted HR 1.19 [0.71−2.00], 1.04 [0.57−1.90], and 2.00 [0.85−4.70], and respectively). There was no interaction between time to thrombolytic therapy and stroke severity on the risk of nursing home admission (P-value for interaction 0.49).

Death

The absolute 1-year risk of death overall was 4.0% (3.5−4.6%). The absolute 1-year risk of death was 2.6% (1.6−4.0%) in the ≤90 min group, 4.2% (3.5−5.1%) in the 91−180 min group, 4.3% (3,3−5.6%) in the 181−270 min group, and 4.7% (2.2−8.7%) in the >270 min group (Fig. 2b). Compared with thrombolytic therapy received ≤90 min of symptom-onset, time to thrombolytic therapy between 91−180 min, and >270 min was not associated with a significantly higher risk of death (adjusted HR 1.58 [0.94−2.65] and 1.49 [0.61−3.63] respectively), though time to thrombolytic therapy between 181−270 min was associated with a significantly higher risk of death (adjusted HR 1.90 [1.08−3.33]).

Factors associated with nursing home admission or domiciliary care initiation

Increasing stroke severity, endovascular therapy, advanced age, living alone, a history of ischemic stroke, atrial fibrillation, diabetes, and chronic kidney disease

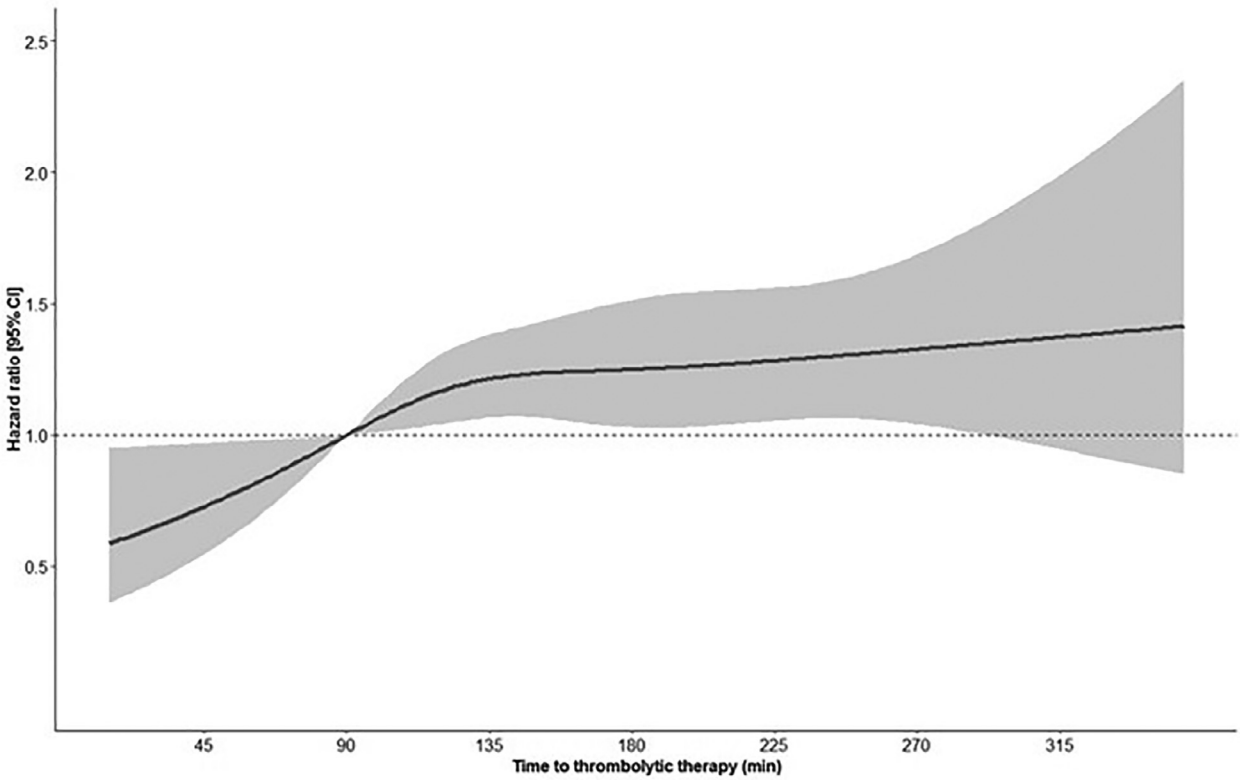

Fig. 3. *Association between time to thrombolysis and risk of nursing home admission or domiciliary care initiation. Restricted cubic splines regression of the association of time to thrombolytic therapy and risk of nursing home admission or domiciliary care initiation. The model was adjusted for age, sex, stroke severity, and endovascular therapy. 90 min was used as a reference. Gray lines indicate 95%CIs.*

were associated with a significantly higher risk of the composite endpoint, whereas higher income was associated with a lower risk of the composite endpoint (Fig. 4).

Discussion

In this nationwide cohort study, we examined the risk of nursing home admission and domiciliary care initiation among all Danish residents admitted with acute ischemic stroke according to time to intravenous thrombolysis. Our study yielded three major findings: First, the absolute 1-year risks of the composite endpoint (i.e. nursing home admission or domiciliary care initiation) and nursing home admission were 13.9% and 2.6%, respectively. Second, time to thrombolysis between 91−180 min and 181−270 min was associated with a significantly increased risk of the composite of nursing home admission or domiciliary care initiation compared with thrombolysis received ≤90 min. Third, advanced age, increasing stroke severity, living alone, a history of ischemic stroke, atrial fibrillation, diabetes, and chronic kidney disease were associated with a higher risk of the composite of nursing home admission or domiciliary care initiation, whereas higher income was associated with a lower risk.

Time to thrombolytic therapy

It is well-established that earlier thrombolytic therapy is associated with improved outcomes in patients presenting with acute ischemic stroke.[4−8] A meta-analysis of individual patient data from randomized trials including 6,756 patients demonstrated 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 months.[4] However, although accumulating evidence from randomized trials and observational studies suggests that treatment delay alters the beneficial effect of thrombolytic therapy in patients presenting with acute ischemic stroke, outcome assessment has primarily focused on mortality, degree of disability, and functional independence.[4−8] In an observational study using data from the US national Get With The Guidelines−Stroke registry, earlier thrombolytic treatment was associated with reduced in-hospital mortality and higher rates of independent ambulation at discharge and discharge to home among 58,353 patients with stroke treated with thrombolytic therapy within 270 min of symptom-onset.[6] However, the discharge status may not fully appraise the long-term consequences of a stroke, and professional assistance to carry out daily life

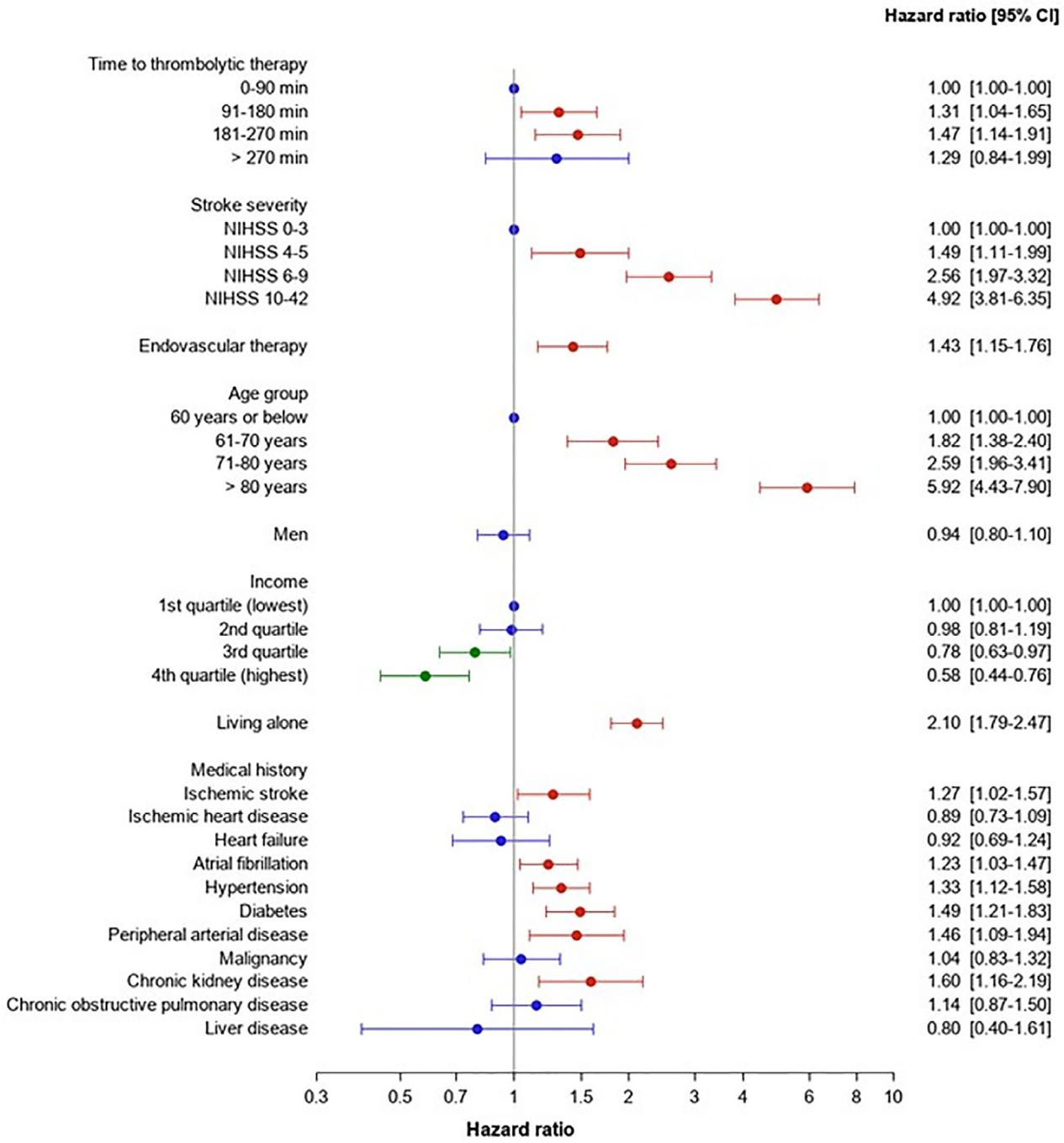

Fig. 4. *Factors associated with nursing home admission or domiciliary care initiation.*

activities in the following year after discharge may perhaps be a more complete metric of downstream consequences of a stroke. Also, this study did not report data on the initiation of domiciliary care support,[6] which represents an additional important metric of quality of care with significant economic consequences for society and personal implications for the individual. While previous studies have shown that early assessment of stroke severity correlates with 3-month outcomes,[22,23] the evaluation of nursing home admission and domiciliary care initiation provides additional insights on the importance of time to initiation of intravenous thrombolytic therapy on post-discharge outcomes. In the present study, time to thrombolysis between 91−180 min and 181−270 min was associated with a significantly increased risk of the composite of nursing home admission or domiciliary care initiation compared with thrombolysis received ≤90 min. These findings were supported by the restricted cubic spline analysis. Although time to thrombolysis >270 min was associated with a numerically higher risk of the composite

endpoint, this association did not reach statistical significance, and this is most likely due to lack of power, given that only 146 patients (3.4% of the total population) received thrombolytic therapy >270 min of symptom-onset. Likewise, although time to thrombolysis between 91−180 min, 181-270 min, and >270 were associated with a numerically higher risk of nursing home admission compared with thrombolysis ≤90 min, these associations were not statistically significant. Taken together, our findings support and extend the available data regarding the association between time to thrombolytic therapy and subsequent outcomes and thus emphasize the importance of early revascularization in eligible patients with acute ischemic stroke. Therefore, continued efforts to shorten the time delay from symptom-onset to initiation of thrombolytic therapy are warranted, including increasing public awareness of stroke symptoms, faster activation of emergency medical systems by patients or bystanders, rapid prehospital triage and transport to a stroke unit, and expeditious evaluation and administration of thrombolysis and/or endovascular therapy in eligible patients.[6]

Factors associated with nursing home admission or domiciliary care initiation

Identifying patients at particular high risk of poor outcomes may have important implications for preventive efforts. Consistent with other studies,[24−27] this study demonstrated that a history of atrial fibrillation and diabetes were associated with worse outcomes despite adjustment for age, stroke severity, and several comorbidities. Although the mechanistic pathways underlying the difference in outcomes of ischemic stroke in patients with and without atrial fibrillation and diabetes remain to be explored, these findings underline the potential importance of appropriate management of diabetes with novel glucose-lowering drugs and atrial fibrillation with oral anticoagulants. In addition, a history of ischemic stroke and increasing stroke severity was strongly associated with higher risk of the composite of nursing home admission or domiciliary care. 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 carry out activities of daily living and manage independently at home.[28−32]

An interesting observation of this study was that living alone was associated with a higher risk of nursing home admission or domiciliary care initiation. This finding emphasizes the importance of spousal support, both in terms of social support and assistance in carrying out activities of daily living. Not surprisingly, this study also demonstrated that advanced age was associated with the need for nursing home and domiciliary care as elderly. Possible explanations for this observation include a greater comorbidity burden, more severe cognitive and physical deficits, and prolonged recovery among elderly patients.

Strengths and limitations

The main strength of this study is the completeness of data in a nationwide unselected cohort of patients with ischemic stroke treated with thrombolytic therapy followed in a real-world setting. Our study has several limitations that need to be acknowledged. The observational nature precludes the assessment of cause-effect relationships, and the possibility of residual confounding cannot be excluded despite rigorous adjustment for potential confounders, including age, sex, income, living alone, comorbidities, and stroke severity, and it is likely that these adjustments were not sufficient to even out all differences between the groups. To assess the potential contribution of unmeasured confounding, we calculated E-values, defined as the minimum strength of association on the risk-ratio scale that an unmeasured confounder would need to have with both the treatment assignment and the outcome to fully explain away a specific treatment-outcome association, conditional on the measured covariates.[33] A large E-value implies that considerable unmeasured confounding would be needed to explain away an effect estimate, whereas a small E-value implies that little unmeasured confounding would be needed to explain away an effect estimate. For the primary outcome, the E-values for the 91−180 min, 181−270 min, and >270 min groups, compared with the <90 min group, were 1.9, 2.3, and 1.9, respectively. Data on important determinants of nursing home admission or domiciliary care initiation, including activities of daily living prior to admission and the degree of cognitive deficits at discharge, were not available. Data on the extent and type of domiciliary care are not sufficiently registered and not available to study. Thus, the need for domiciliary care reflects a wide spectrum of need for care. 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 and the population is predominantly white. This should be considered when translating our findings to countries with more restricted access to these services and more heterogeneous populations with respect to ethnicity.

Conclusions

In a Danish nationwide all-comers cohort of patients admitted with acute ischemic stroke and treated with intravenous thrombolytic therapy, time to thrombolysis between 91−180 min and 181−270 min was associated with a significantly increased risk of the composite of nursing home admission or domiciliary care initiation compared with thrombolysis received ≤90 min. Continued efforts to shorten the time delay from symptom-onset to initiation of thrombolytic therapy are warranted.

Sources of Funding

None.

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.

Declaration of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2021.105916.

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