Hindawi
Acta Neurologica Scandinavica
Volume 2024, Article ID 8805152, 11 pages
https://doi.org/10.1155/2024/8805152

Research Article

Estimates and Predictors of Mortality, Stroke Recurrence, and Functional Dependency 1-Year after Ischemic Stroke: A Prospective Multicenter Longitudinal Cohort Study in Central Norway

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Received 25 September 2023; Revised 4 April 2024; Accepted 13 April 2024; Published 3 May 2024

Academic Editor: Carlo Colosimo

Background. Stroke incidence and mortality have drastically decreased in high-income countries in the past twenty years. In this study, we provide updated estimates on mortality, recurrent stroke, and functional dependency among patients with first-ever ischemic stroke and assess predictors associated with poor outcomes with a focus on age, vascular factors, stroke severity, function, and comorbidity burden. *Methods*. MIDNOR STROKE is a multicenter prospective longitudinal study including patients with first-ever ischemic stroke admitted to stroke units in Central Norway during 2015-2017. Data on survival, stroke recurrence, and functional dependency were collected during hospital stay and follow-up. Multivariable Cox proportional hazard models and logistic regression models were used to analyze predictors of mortality, stroke recurrence, and functional dependency. *Results*. A total of 794 participants were included in the study. After a year, 7.6% of the participants had died, 5.8% had a recurrent stroke, and 13.6% experienced functional deterioration to dependency. Multivariable analysis revealed that age (HR: 1.07, 96% CI: 1.03, 1.10), stroke severity (HR: 1.10, 95% CI: 1.07, 1.13), comorbidity burden (low: HR: 4.05, 95% CI: 1.48, 11.10; moderate: HR: 5.44, 95% CI: 2.06, 14.40; and high: 7.72, 95% CI: 2.85, 21.00), and coronary artery disease (HR: 2.40, 95% CI: 1.32, 4.38) predicted all-cause death. Statin therapy predicted improved survival (HR: 0.39, 95% CI: 0.21, 0.75). High age (HR: 1.09, 95% CI: 1.05, 1.14) and increased stroke severity (OR: 1.26, 95% CI: 1.17, 1.38) predicted elevated risk of functional dependency at one year. *Conclusions*. In this study, we have demonstrated that 1-year survival following first-ever ischemic stroke was high compared to previous reports and that statin therapy predicted improved survival. The risk of recurrent stroke after one year was found to be low compared to previous studies. Approximately 14% of stroke survivors who were initially functionally independent experienced deterioration to functional dependency. In addition to older age and stroke severity, increased comorbidity burden and a history of coronary artery disease predicted poor stroke prognosis. Interventions aimed at reducing stroke severity may improve patient outcomes. Furthermore, prevention efforts targeting conditions such as CAD and reducing overall comorbidity burden in stroke patients may favorably improve survival. This trial is registered with NCT03962127.

1. Background

Stroke prognosis has improved remarkably in high-income countries in the last decades [1]. In Norway, there has been a notable decline in stroke incidence rates over the previous 20 years, accompanied by a 44% decrease in stroke mortality in the last decade [2, 3]. Despite these advancements, stroke remains a significant cause of mortality, ranking as the second-leading cause of death globally and the third-leading cause of both death and disability combined [1]. Additionally, with population aging and enhanced survival rates, the absolute number of strokes and stroke survivors is expected to rise. The significant improvements in stroke outcomes can be attributed to better management of vascular risk factors, adoption of healthier lifestyles, improved acute treatment, rehabilitation, and prevention strategies [4–6]. However, previous studies have had limited sample sizes, follow-up periods, and highly varying estimates of death, recurrent stroke, and functional recovery within the first year post-stroke [7–9]. Furthermore, ischemic stroke patients typically represent a heterogeneous population characterized by multiple vascular risk factors, comorbidities, and physical disabilities [1, 8, 10, 11]. This diversity presents challenges for the comprehensive assessment of factors influencing stroke outcomes.

There is substantial evidence supporting the role of managing cardiovascular risk factors in reducing the risk of stroke [12]. Hypertension, smoking, diabetes mellitus, dyslipidemia, unhealthy diet, obesity, physical inactivity, and atrial fibrillation are among the most prevalent and influential modifiable risk factors for stroke [1, 12, 13]. Previous research has also highlighted patient age, functional status, stroke severity, cardiovascular diseases, and comorbidity burden as significant prognostic factors for stroke mortality and functional dependency [7, 8, 11, 12, 14–16].

However, the impact of these factors may have changed in recent decades due to advances in stroke prevention, treatment, and lifestyle changes. Furthermore, recent data on risk estimates of poor outcomes and prognostic factors for stroke in the Norwegian population is lacking.

Given recent developments in stroke incidence and treatment, there is a need to reassess risk factors associated with mortality, stroke recurrence, and disability and update estimates accordingly. Information on long-term outcomes and factors associated with poor outcomes can aid in identifying high-risk patients and in optimizing prevention strategies and follow-up after stroke. In this study, we aim to provide updated estimates on mortality, recurrent stroke, and functional dependency after first-ever ischemic stroke. Furthermore, we seek to identify predictors of poor outcome before the index stroke and those related to stroke prevention, with a particular focus on age, function, stroke characteristics, vascular risk factors, and comorbidity burden.

2. Methods

2.1. Study Design. MIDNOR STROKE is an ongoing prospective longitudinal multicenter cohort study following patients with first-ever ischemic stroke in Central Norway. The primary objective of MIDNOR STROKE was to establish a cohort of patients with first-ever ischemic stroke, with the overall aim of obtaining knowledge on how to improve survival, maintain good physical and mental health, and increase the quality of life after stroke.

Patients were recruited from stroke units at the following eight hospitals: St. Olav, Molde, Levanger, Namsos, Volda, Kristiansund, Ålesund, and Orkdal. These hospitals serve a catchment area of approximately 700 000 inhabitants and are the care providers for the acute treatment of all stroke patients in Central Norway.

Between June 1, 2015, and November 1, 2017, 815 patients were consecutively recruited. Participants had to meet the following inclusion criteria: cerebral infarction according to the World Health Organization criteria and ICD-10 DM diagnosis code I63 [17], ≥18 years of age, first-ever stroke, residency in Central Norway, and recruitment within 7 days of symptom onset. Patients were excluded if their focal neurological symptoms were later determined not to be stroke-related or if the patient had severe disabilities prior to the stroke, defined as modified Rankin scale (mRS) score of 5. Complications during hospital stay included seizures, falls, serious infections, and neurological progression.

MIDNOR STROKE was approved by the Regional Research Ethics Committee in 2015. In our study, all participants received standard care and treatment in accordance with the national recommended guidelines for the treatment and rehabilitation of stroke [18]. Participation in the study was voluntary and required informed consent. Patients unable to provide consent themselves were recruited with informed consent from a family member or caregiver.

2.2. Data Collection. Data were collected during the initial hospital stay and at outpatient follow-up at 3 months by clinical examinations, questionnaires, and physical assessments and by review of medical journals. Data gathered at 12 months were collected by phone interviews and questionnaires. Collected data included demographic factors, previous medical history, patient care and status during hospital stay, stroke characteristics, blood tests, functional assessments, and medication at discharge. Data on hospital readmission and medications at discharge were additionally retrieved from the Norwegian Stroke Registry, while information on deaths was obtained from the Norwegian Death Registry.

2.3. Outcomes and Independent Variables. The primary outcomes were all-cause death, stroke recurrence, and functional dependency within a year after stroke onset. *Stroke recurrence* was defined as any hospitalized stroke event (ICD-10 I60, I61, I63, and I64) following the index stroke. Time of death and recurrent strokes were collected for all participants. Functional outcome was assessed by the modified Rankin scale (mRS) during follow-up at 1 year by phone interview. *Functional dependency* was defined as an mRS score of 3-5 [19].

The impact of comorbidity burden on poor outcomes (death, stroke recurrence, or functional dependency) was assessed by the Charlson comorbidity index (CCI) [20].

Stroke characteristics were described by stroke severity measured at day 1 after admission to hospital by the National Institutes of Health Stroke Scale (NIHSS) [21], while stroke etiology was determined by the Trial of Org 10172 in Acute Stroke Treatment (TOAST) [22]. *Hypertension* was defined as having been prescribed antihypertensive drugs prior to hospital admission or at discharge and included calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, or diuretics. *Statin therapy* was defined as lipid-lowering drugs prescribed prior to admission and at discharge. Diabetes mellitus (DM) was defined as having been prescribed antidiabetic drugs prior to hospital admission, at discharge or HbA1c $\geq 6.5\%$ during hospital stay, and *coronary artery disease* (CAD) was defined as having a history of myocardial infarction or angina pectoris.

2.4. Statistical Analysis. Continuous variables are reported as mean and standard deviation, while categorical variables are reported as frequencies and percentages. Kaplan-Meier estimates for the cumulative risk of all-cause death and stroke recurrence were calculated for a 1-year period. Participants who died during follow-up were censored in the Kaplan-Meier analysis for recurrent stroke. Predictors of interest were selected a priori based on known modifiable risk factors of stroke [7, 12, 18] and data available in the MIDNOR STROKE dataset. Predictors associated with survival and stroke recurrence were assessed with multivariable Cox proportional hazard models, whereas functional dependency was analyzed by logistic regression models. Age-adjusted analyses were performed for selected clinical variables for death, stroke recurrence, and functional dependency. In the multivariable models, age, DM, hypertension, statin therapy, CAD, stroke severity (NIHSS day 1), atrial fibrillation (AF), comorbidity burden, and prestroke function were adjusted. Two multivariable models were analyzed. Model 1 included age, prestroke function (mRS), stroke severity, and vascular risk factors (hypertension, statin therapy, AF, DM, and CAD). In model 2, DM and CAD were omitted as predictors, while the CCI score was included. To determine the risk of functional dependency, participants with mRS scores 0-2 prestroke (functionally independent) were selected for the logistic regression analyses. The proportional hazard assumption in the Cox model was checked using Schoenfeld residual plots. All analyses were performed using available case analysis.

Estimates and 95% confidence intervals (CI) are presented where relevant. Two-sided p values < 0.05 were considered to be statistically significant. All analyses were performed using the survival package v3.2-7 [23] in RStudio version 1.4.1717.

3. Results

A total of 794 patients were included. At 1 year, 115 participants were lost to follow-up at 12 months (see Additional File 1, Figure. S1). The baseline demographics and clinical characteristics of the study population are presented in Table 1. The number of patients on antihypertensive drugs and statins increased after hospitalization for stroke, from 384 (48.4%) to 481 (60.5%) for antihypertensives and from 290 (36.5%) to 661 (83.2%) for statins.

3.1. Mortality. At 1-year follow-up, 60 participants had died. Figure 1 shows Kaplan-Meier curves for mortality and stroke recurrence for all 794 participants. The cumulative risk of death during the first year was 7.6% (95% CI, 5.7-9.4).

Table 2 displays age-adjusted hazard ratios for death and results from the multivariable models. Statistically significant age-adjusted factors were stroke etiology, complications during the hospital stay, comorbidity burden, thrombolysis, stroke severity, statin therapy, and CAD. Cardioembolic strokes were associated with the highest risk of all-cause death, while statin therapy predicted reduced risk. A total of $n = 733$ participants were available for analysis in our multivariable models. In the multivariable models for all-cause death, stroke severity (NIHSS day 1), history of CAD, and comorbidity burden significantly predicted increased risk of death, while statin therapy predicted reduced risk. After adjustment for comorbidity burden, results from our multivariable model showed that functional status (mRS–prestroke) significantly predicted an increased risk of death (Table 2).

Following these findings, we conducted sensitivity analyses. Although complications during hospital stay were not initially included in our multivariable models, a sensitivity analysis (see Additional File 1, Table. S1) revealed that when complications during hospital stay were incorporated into our multivariable models, it predicted a twofold risk of death within 1 year (HR: 2.61, 95% CI: 1.47-4.63, p value: 0.001). Furthermore, we conducted a sensitivity analysis on our age-adjusted model for thrombolysis, incorporating stroke severity to predict the risk of death. Following adjustment for age and stroke severity, thrombolytic treatment was no longer associated with an increased risk of death at 1 year (HR: 1.32, 95% CI: 0.73-2.41, p value: 0.400) (see Additional File 1, Table. S2).

We also performed a sensitivity analysis using hypertension before stroke as a predictor in our multivariable analysis. These data revealed that hypertension before stroke significantly predicted an increased risk of death (HR: 2.54, 95% CI: 1.29-4.98, p value: 0.007; see Additional File 1, Table. S3).

3.2. Stroke Recurrence. At 1-year follow-up, 46 participants had experienced a recurrent stroke. The cumulative recurrent rate was 5.8% at one year (95% CI, 4.3-7.7) (Figure 1). In our multivariable models, $n = 737$ subjects were available for analysis. Our age-adjusted and multivariable models revealed no statistically significant associations between clinical risk factors of interest and stroke recurrence (Table 3).

3.3. Functional Dependency. Following 1 year, functional assessment of the surviving participants showed that 22.5% (events = 138/$n = 613$) were functionally dependent (mRS 3-5). Our data also revealed that 13.6% (events = 73/$n = 536$) of the participants who were functionally independent before the stroke (mRS 0-2) became functionally dependent (mRS 3-5) after the stroke.

Table 1: Baseline characteristics.

	Overall ($N = 794$)
Age (years), mean (SD) [min, max]	73.2 (11.6) [27, 97]
Sex, male	447 (56.3%)
Modified Rankin scale	
Independent 0-2	663 (83.5%)
Dependent 3-4	127 (16.0%)
Missing	4 (0.5%)
Stroke characteristics	
Stroke etiology	
Small vessel occlusion	198 (24.9%)
Large artery atherosclerosis	146 (18.4%)
Cardioembolism	166 (20.9%)
Stroke of other determined etiology	64 (8.1%)
Stroke of undetermined etiology	220 (27.7%)
NIHSS day 1, mean (SD) [min, max]*	3.57 (4.93) [0, 38]
Missing	53 (6.7%)
Cardiovascular risk factors and comorbidities	
Coronary artery disease	167 (21.0%)
Hypertension	384 (48.4%)
Diabetes mellitus	141 (17.8%)
Hypercholesterolemia	290 (36.5%)
Smoking status	
Current smoker	163 (20.5%)
Missing	2 (0.3%)
Charlson comorbidity burden	
0—none	304 (38.3%)
1—low	184 (23.2%)
2-3—moderate	205 (25.8%)
4 or more—high	101 (12.7%)
Patient care parameters and medications at discharge	
Length of hospital stay (days), mean (SD) [min, max]	6.45 (4.9) [0, 42]
Complications during hospital stay	154 (19.4%)
Thrombolytic therapy	170 (21.4%)
Antihypertensive at discharge	481 (60.6%)
Statins at discharge	661 (83.2%)
Antithrombotic therapy at discharge	767 (96.6%)

*National Institutes of Health Stroke Scale (NIHSS).

Age-adjusted analysis (Table 4) showed that large artery atherosclerosis (OR: 2.75, 95% CI: 1.19-6.57) and cardioembolic strokes (OR: 3.14, 95% CI: 1.45-7.14) compared to small vessel disease predicted increased risk of functional dependency. In our multivariable models, $n = 499$ participants were available for analysis. Stroke severity, history of CAD, and complications during hospital stay also predicted an increased risk of functional dependency. In the multivariable models for functional dependency, age and stroke severity significantly predicted functional dependency 1 year after stroke. Although not statistically significant, our multivariable analyses indicated that a history of coronary artery disease and high comorbidity burden were associated with increased risk of functional dependency.

Our sensitivity analysis of participants with complications revealed that patients who experienced complications during hospital stay were, on average, older and had a higher proportion of vascular risk factors present and a higher degree of comorbidity burden than patients without any complications (see Additional File 1, Table. S4).

4. Discussion

In a cohort of first-ever ischemic stroke patients included from all stroke units in Central Norway, 7.6% died, 5.8% had a recurrent stroke, and 13.6% transitioned from functional independency before stroke to dependency during the 1-year follow-up period. This study showed that age,

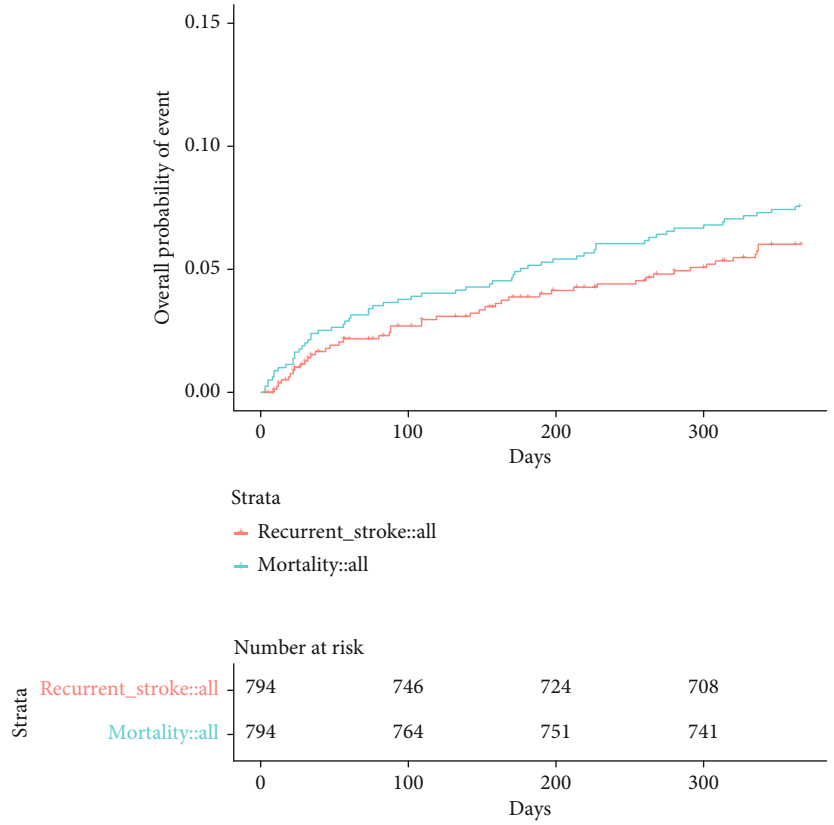

Figure 1: Kaplan-Meier curves for mortality and stroke recurrence after first-ever ischemic stroke at 1 year.

stroke severity, comorbidity burden, and a history of CAD significantly predicted death and disability at 1 year and that statin therapy was associated with improved survival.

4.1. Incidence Rates of Stroke Mortality and Recurrence. Compared to past reports, the mortality rate at 1 year following first-ever ischemic stroke was low in our study population [8, 24–28]. Our estimated mortality rate of 7.6% is comparable with results from two large prospective studies, where estimates of all-cause death varied between 6.8 and 8.6% [27, 29]. However, it is important to note that previously reported mortality rates vary greatly. Differences in 30-day mortality rates across European countries are notable, with Norway standing out for its low case fatality rates following hospital admission [30].

Our estimated stroke recurrence rate of 5.8% at 1 year is comparable to a study reporting a cumulative recurrence rate of 5.4% in stroke patients in Western Norway [31]. Both estimates are considerably lower than the pooled recurrence rate found in Lin et al.'s meta-analysis, where it was estimated at 10.4% (95% CI 8.9–11.9%) for studies conducted between 2010 and 2019 [32].

Comparing previous reports on mortality rates and recurrent stroke is challenging due to variations in age, risk factors, stroke treatment, and prevention strategies. Our study's low mortality rate can partly be attributed to the low incidence of recurrent strokes. It may also reflect that the majority of our study population had mild strokes (82.2%, NIHSS ≤ 5) and experienced fewer complications during their hospital stay compared to other studies [33]. As indicated by previous studies [34, 35], improved control of vascular risk factor has most likely contributed to the low stroke recurrence and overall mortality observed in our study population. Additionally, all participants received stroke unit care which is well documented to reduce death and disability within the first year after stroke [36].

4.2. Predictors of Stroke Mortality and Recurrence. Consistent with previous studies [8, 37–39], our study demonstrated that age, stroke severity, and CAD were strong prognostic factors of mortality. Furthermore, our study showed that statin therapy was associated with improved survival 1 year after stroke. Although we cannot confirm the cause of death, it is likely that statins contributed to better survival by reducing the risk of fatal myocardial infarction and potentially fatal strokes, as previously indicated by Amarenco and Labreuche [40]. The effect of statins may be mediated through lipid lowering, plaque stabilization, and various neuroprotective effects [41].

Although hypertension is considered a major factor in determining risk of stroke and overall mortality [42, 43], we did not observe such associations at 1 year. Our findings suggest that patients diagnosed with hypertension prior to hospital admission were at higher risk of death compared to patients diagnosed during hospital stay. We suspect that

Table 2: Cox age-adjusted and multivariable proportional hazards models for death. In the multivariable models, the total number of available cases was $n = 737$ and events $n = 57$.

Characteristic	Age-adjusted			Multivariable model 1			Multivariable model 2		
	HR[1]	95% CI[2]	p value	HR[1]	95% CI[2]	p value	HR[1]	95% CI[2]	p value
Age (years)	1.11	1.07-1.14	<0.001	1.07	1.03-1.10	<0.001	1.07	1.03-1.11	<0.001
Male	1.30	0.78-2.18	0.30	1.33	0.73-2.43	0.30	1.50	0.82-2.74	0.20
Modified Rankin scale									
Dependent 3-4	0.88	0.47-1.61	0.70	0.61	0.31-1.20	0.20	0.50	0.25-1.00	0.05
Stroke etiology			0.045						
Small vessel occlusion	—	—							
Large artery atherosclerosis	2.97	1.06-8.36							
Cardioembolism	3.67	1.38-9.76							
Stroke of other determined etiology	3.53	1.02-12.20							
Stroke of undetermined etiology	2.21	0.80-6.11							
Complications during hospital stay	3.31	1.99-5.52	<0.001						
Thrombolysis	1.85	1.06-3.21	0.030						
NIHSS day 1[†]	1.10	1.07-1.13	<0.001	1.10	1.07-1.13	<0.001	1.09	1.06-1.12	<0.001
Charlson comorbidity burden			<0.001						<0.001
0—none	—	—					—	—	
1—low	4.05	1.48-11.10					5.56	1.94-15.90	
2-3—moderate	5.44	2.06-14.40					6.82	2.49-18.60	
4 or more—high	7.75	2.85-21.00					6.89	2.44-19.50	
Atrial fibrillation	1.63	0.97-2.74	0.065	1.04	0.58-1.87	0.90	0.96	0.52-1.78	0.90
Antihypertensive	0.90	0.53-1.51	0.70	0.71	0.40-1.26	0.20	0.61	0.34-1.10	0.10
Statin therapy	0.40	0.22-0.71	0.002	0.39	0.21-0.75	0.004	0.39	0.20-0.76	0.006
Diabetes mellitus	1.20	0.65-2.21	0.60	1.39	0.70-2.76	0.30			
Current smoker	1.06	0.50-2.27	0.90						
CAD[§]	1.79	1.06-3.02	0.029	2.40	1.32-4.38	0.004			

[1]HR = hazard ratio; [2]CI = confidence interval. [†]National Institutes of Health Stroke Scale (NIHSS). [§]Coronary artery disease (CAD).

optimal blood pressure treatment at discharge may explain the lack of effect of hypertension as a risk factor. Conversely, the increased risk of death among hypertensive patients upon admission may stem from suboptimal BP treatment before stroke.

In our study, we found that contrary to previous studies [25, 26, 29, 44], AF and DM were not predictors of overall mortality in our study. This may be explained by the use of anticoagulants in nearly all participants with AF in our study, as well as optimal risk factor control in diabetic patients, as supported by population data [4].

In our study, we found that high comorbidity burden predicted all-cause mortality. This finding aligns with previous results [14, 15, 45], which demonstrated an increased risk of all-cause mortality as comorbidity scores increased. Additionally, our findings support previous data showing that individuals with pre-existing functional disabilities before a stroke have an elevated risk of all-cause death [11]. This elevated risk persists even after accounting for comorbidity burden, as demonstrated in our multivariable analyses.

Our results confirm prior data on ischemic stroke subtypes determined by the TOAST criteria as a significant predictor for survival, with the highest risk of mortality observed in patients with cardioembolic strokes [46].

Complications during hospitalization are recognized as contributing factors to adverse outcomes after stroke [33, 47]. Our study further demonstrated that these complications play a significant role in predicting survival at 1 year.

Contrary to previous research [7, 12, 31], our study did not find any associations between age, vascular risk factors, and stroke recurrence. One possible explanation for these observations is that the patients in our study population benefited from optimal secondary prevention. We also suspect that the absence of significant associations between selected vascular factors and stroke recurrence is primarily due to the low incidence of recurrent strokes and the relatively short follow-up period.

4.3. Functional Dependency 1-Year Poststroke. Prior data on the prevalence of functional dependency at 1 year ranges between 12 and 37%. In a large study by Ullberg et al., they reported 23% and 35% ADL dependency for men and women, respectively, and 16% deterioration of ADL dependency at 12 months [8, 48, 49]. Although we did not use the same measure of functional outcome, our study similarly revealed a prevalence of functional dependency of 22.4% 1 year after a stroke, with functional deterioration to dependency occurring in 13.6% of the cases.

Table 3: Cox age-adjusted and multivariable proportional hazards models for stroke recurrence. In the multivariable models, the total number of available cases in the multivariable analyses was $n = 737$ and events $n = 45$.

Characteristic	Age-adjusted			Multivariable model 1			Multivariable model 2		
	HR[1]	95% CI[2]	p value	HR[1]	95% CI[2]	p value	HR[1]	95% CI[2]	p value
Age (years)	1.01	0.99-1.04	0.30	1.02	0.99-1.05	0.30	1.01	0.98-1.04	0.50
Male	1.52	0.82-2.80	0.20	1.44	0.76-2.73	0.30	1.16	0.61-2.20	0.60
Modified Rankin scale									
Dependent 3-4	0.67	0.27-1.65	0.40	0.65	0.25-1.70	0.40	0.60	0.23-1.55	0.30
Stroke etiology			0.80						
Small vessel occlusion	—	—							
Large artery atherosclerosis	1.70	0.67-4.31							
Cardioembolism	1.50	0.59-3.83							
Stroke of other determined etiology	1.68	0.51-5.60							
Stroke of undetermined etiology	1.61	0.68-3.84							
Complications during hospital stay	1.42	0.71-2.83	0.30						
Thrombolysis	1.71	0.91-3.21	0.094						
NIHSS day 1[†]	0.99	0.92-1.06	0.70	0.99	0.92-1.06	0.80	0.99	0.93-1.07	0.90
Charlson comorbidity burden			0.064						0.078
0—none	—	—					—	—	
1—low	1.36	0.56-3.30					1.24	0.49-3.11	
2-3—moderate	2.38	1.11-5.10					2.36	1.08-5.16	
4 or more—high	2.65	1.09-6.48					2.58	1.03-6.46	
Atrial fibrillation	1.43	0.75-2.74	0.30	1.53	0.78-3.01	0.20	1.40	0.71-2.74	0.30
Antihypertensive	1.29	0.69-2.40	0.40	1.17	0.62-2.24	0.60	1.06	0.56-2.02	0.80
Statin therapy	0.93	0.42-2.05	0.90	0.81	0.35-1.91	0.60	0.86	0.37-1.99	0.70
Diabetes mellitus	1.30	0.64-2.61	0.50	1.40	0.67-2.90	0.40			
Current smoker	1.45	0.74-2.86	0.30						
CAD[§]	0.76	0.35-1.64	0.50	0.61	0.27-1.38	0.20			

[1]HR = hazard ratio, [2]CI = confidence interval. [†]National Institutes of Health Stroke Scale (NIHSS). [§]Coronary artery disease (CAD).

This study confirms prior data on age, stroke severity, and complications during hospital stay as major prognostic factors for functional outcome after stroke [8, 50]. While numerous predictors of functional dependency have been proposed, no studies have assessed the impact on functional dependency in a comprehensive model that includes vascular risk factors, stroke severity, and comorbidity burden. Although comorbidity burden did not reach statistical significance ($p = 0.055$), our results suggest that patients with an increased comorbidity burden are at higher risk of functional dependency poststroke. This observation may be influenced by the relatively high proportion of individuals with none and low comorbidity burden in our study cohort. It is worth noting that previous studies have shown inconsistent results, likely due to variations in the use of modified versions of the CCI [14].

Despite evidence indicating the negative impact of DM, AF, and CAD [7, 14] on functional outcome poststroke, none of these vascular risk factors in our multivariable models showed significant associations with functional dependency at 1 year. We suspect that this lack of association may be attributed to the high number of patients with mild strokes in our study population and the low incidence of recurrent strokes. Furthermore, our findings may suggest that vascular risk factors are more important to the development of stroke rather than in determining functional prognosis following a stroke.

Our age-adjusted analysis supports prior data on patients with LAA and CE strokes with poorer long-term prognosis when it comes to functional outcome. Better functional outcome is often more seen in patients with small vessel disease, which compared to LA and CE strokes, commonly is associated with smaller infarct size [51].

4.4. Strengths and Limitations. Our study had several strengths. Firstly, the multicenter design, with patients recruited consecutively from stroke units at all eight hospitals in Central Norway, which is a geographic well-defined area, allows for the assumption that our results may be applied to the general population of first-ever ischemic stroke patients in Norway. Secondly, our study had a high degree of completeness and quality, with information collected from patient follow-up, complemented by data from medical journals and patient registries. This allowed for a comprehensive assessment of risk factors related to poor outcomes.

Our study also had limitations. The number of participants experiencing a recurrent stroke event was small. For

Table 4: Age-adjusted and multivariable logistic regression models for functional dependence (mRS 3-5). The total number of available cases in the multivariable analyses was $n = 499$ and events $n = 67$.

Characteristic	Age-adjusted			Multivariable model 1			Multivariable model 2		
	OR[1]	95% CI[2]	*p* value	OR[1]	95% CI[1]	*p* value	OR[1]	95% CI[2]	*p* value
Age (years)	1.12	1.10-1.15	<0.001	1.09	1.05-1.14	<0.001	1.10	1.06-1.15	<0.001
Male	0.75	0.45-1.28	0.30	0.69	0.36-1.30	0.30	0.78	0.42-1.48	0.40
Stroke etiology			0.016						
Small vessel occlusion	—	—							
Large artery atherosclerosis	2.75	1.19-6.57							
Cardioembolism	3.14	1.45-7.14							
Stroke of other determined etiology	2.84	0.99-7.89							
Stroke of undetermined etiology	1.37	0.58-3.31							
Complications during hospital stay	3.57	1.93-6.53	<0.001						
Thrombolysis	0.60	0.27-1.19	0.20						
NIHSS Day 1[†]	1.27	1.18-1.38	<0.001	1.26	1.17-1.38	<0.001	1.29	1.19-1.41	<0.001
Charlson comorbidity burden			0.086						0.055
0—none	—	—					—	—	
1—low	2.24	1.15-4.39					2.71	1.25-5.96	
2-3—moderate	1.50	0.74-3.02					1.82	0.78, 4.21	
4 or more—high	2.14	0.90-4.92					2.57	0.92-6.94	
Atrial fibrillation	1.58	0.88-2.77	0.11	1.00	0.48-1.97	>0.90	0.98	0.47-1.94	>0.90
Antihypertensive	1.35	0.78-2.42	0.30	1.39	0.71-2.84	0.30	1.47	0.76-2.96	0.30
Statin therapy	0.64	0.29-1.52	0.30	1.03	0.40-2.95	>0.90	1.01	0.39-2.90	>0.90
Diabetes mellitus	1.56	0.82-2.87	0.20	1.21	0.54-2.61	0.60			
Current smoker	1.08	0.50-2.17	0.80						
CAD[§]	1.87	1.03-3.34	0.036	2.03	0.99-0.4.13	0.052			

[1]OR = odds ratio; [2]CI = confidence interval. [†]National Institutes of Health Stroke Scale (NIHSS). [§]Coronary artery disease (CAD).

that reason, our analysis may have failed to detect true effects. Additionally, functional assessments from 115 participants were missing due to lost to follow-up during the first year. We suspect that these data were not missing at random, and those not included in our analysis were either at very good health following the stroke, or among the severely ill. Furthermore, hospital-based populations typically include patients who have sought medical care and have been admitted to hospitals. These patients may have milder stroke or fewer comorbidities compared to those who do not seek medical attention or die before reaching hospital. This may also hold true for our study sample, which could lead to a biased prognosis of stroke. Another unavoidable limitation is our limited follow-up time and the exclusion of patients with an mRS score of 5 and recurrent strokes. Furthermore, the absence of data on acute treatment, rehabilitation, drug compliance, or cause of death limits the interpretation of our predictors.

5. Conclusions

In this study, we demonstrated that survival following first-ever ischemic stroke at 1 year was high compared to past reports and that preventive statin treatment predicted improved survival. The risk of recurrent stroke after 1-year was found to be low compared to previous findings. Approximately 14% of stroke survivors who were initially independent experienced functional dependency. In addition to older age and stroke severity, an increased comorbidity burden and a history of coronary artery disease predicted poor stroke prognosis. Further research on comprehensive risk factor reduction to improve outcome after stroke is needed, and causal relationships remain to be explored.

6. Clinical Implications

These findings may have clinical implications for the management of patients following first-ever ischemic stroke. The observed association between preventive statin treatment and improved survival at 1 year underscores the importance of optimal initiation and maintenance of statin therapy to improve stroke outcome. Interventions aimed at reducing stroke severity may improve patient outcome. Furthermore, prevention efforts targeting conditions such as CAD and reducing overall comorbidity burden in stroke patients may favorably improve survival.

Abbreviations

ADL: Activities of daily living
AF: Atrial fibrillation
BP: Blood pressure
CAD: Coronary artery disease
CCI: Charlson comorbidity index

CI: Confidence intervals
CVD: Cardiovascular diseases
DM: Diabetes mellitus
mRS: Modified Rankin scale
NIHSS: National Institutes of Health Stroke Scale
TOAST: Trial of Org 10172 in Acute Stroke Treatment.

Data Availability

The datasets generated and analyzed during the current study are not publicly available due to local and legal restrictions. A portion of the data can be made available upon reasonable request and if approval from the Regional Committee of Medical and Health Research Ethics Western Norway is granted. Requests to access the datasets should be directed to the corresponding author Ailan Phan (ailan.phan@ntnu.no).

Ethical Approval

This study was carried out according to the Declaration of Helsinki. This study was approved by the Regional Committee of Medical and Health Research Ethics Western Norway (2015/453/REK midt).

Consent

Participation in the study was voluntary and required written informed consent from all participants. Patients who were not able to provide consent were recruited if informed consent was obtained from their proxy (family member or caregiver).

Disclosure

The funders of the study had no role in study design, data collection, data interpretation, or writing of the manuscript.

Conflicts of Interest

The authors declare that they have no competing interests.

Authors' Contributions

AP, BI, and TW contributed to the conception and design. ÅM, YS, and BI were responsible for patient recruitment, assessment, and data collection at their respective hospitals. BI, TW, ÅM, YS, and FI provided input on the interpretation of patient data. AP wrote the study protocol, participated in collecting data, performed the statistical analysis, interpreted the patient data, and wrote the draft of the paper. SL provided guidance and statistical input to the analyses. All authors have read and approved the final manuscript.

Acknowledgments

We thank the participants, study nurses, physicians, and other colleagues at the collaborating hospitals, Namsos, Ålesund, Volda, Kristiansund, Orkdal, Levanger, Molde, and St. Olavs, who participated in the study and Torstein Storflor Hegge for the discussion on the analysis of data. The MIDNOR STROKE study was funded by The Liaison Committee for education, research and innovation in Central Norway and the Foundation DAM. Open Access funding was enabled and organized by SIKT GOLD.

Supplementary Materials

Additional file 1: Supplementary tables S1-S4, Supplementary figure S1. *(Supplementary Materials)*

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