

# Medical Prophylaxis following Hospitalization for Ischemic Stroke: Age- and Sex-Related Differences and Relation to Mortality

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## Key Words

Age differences · Ischemic stroke · Medical prophylaxis · Sex difference

## Abstract

**Background:** The extent and implications of age- and sex-related differences in prophylaxis following ischemic stroke are unknown. We examined differences in the use of medical prophylaxis across age and sex groups in stroke patients after hospital discharge in Denmark and estimated the possible impact on age- and sex-related differences in mortality. **Methods:** A nationwide population-based follow-up study was conducted involving 28,634 patients hospitalized for ischemic stroke in 2003–2006 who survived 30 days after discharge. The proportion of patients who filled prescriptions for cardiovascular drugs within 0–6 and 12–18 months after discharge was determined. Mortality rates were compared across age and sex groups with and without controlling for use of medical prophylaxis. **Results:** Increasing age was associated with lower prophylaxis. Adjusted odds ratios for the use of a combination of a platelet inhibitor, an antihypertensive and a statin were 0.45 [95% confidence interval (CI): 0.38–0.54] and 0.52 (95% CI: 0.43–0.62) for men and women >80 years, respectively, compared with men ≤65 years. No systematic sex-related differences were identified. Contin-

ued drug use ranged from 66.1 to 91.9% for different drugs 12–18 months after discharge, with the lowest rate of continued use found among patients >80 years. Controlling for use of medical prophylaxis was associated with lower mortality rate ratios for elderly compared with younger patients. **Conclusions:** Continuous efforts are warranted to ensure implementation of evidence-based secondary prophylaxis among elderly patients with ischemic stroke.

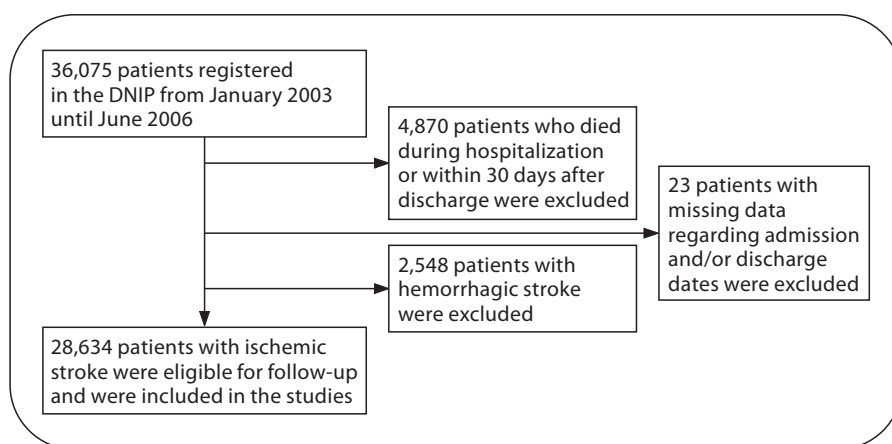
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## Introduction

Although stroke is a serious clinical event irrespective of age and sex [1], there are striking differences in outcome, including mortality and functional level, according to age and sex [2–9]. In general, younger stroke patients have a better outcome, i.e. lower mortality and higher functional level [10–12], than older patients; similarly, women appear to have better outcomes than men.

A number of studies have found that older patients (≥65 years) and women receive poorer in-hospital care

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**Fig. 1.** Flow chart for the study population.

compared to younger patients and males [3–6, 8, 9]. However, other studies have failed to confirm these differences in acute care, and the effects of such differences on patient outcome may be modest [5, 13].

The existence of age- and sex-related differences in stroke care after discharge is even more uncertain. Based on findings from randomized controlled trials, current stroke guidelines recommend that lifelong medical prophylaxis, including antithrombotic, antihypertensive and lipid-lowering therapy, be considered for all patients with ischemic stroke regardless of age and sex [14–16]. A lack of evidence-based medical prophylaxis could potentially have a large impact on patient outcome, so it is of major clinical and public health interest to identify patient groups that are likely to receive inadequate prophylaxis. We therefore aimed to determine whether there are age- and sex-related differences (in terms of use and perseverance) in medical prophylaxis among patients with ischemic stroke in Denmark. We further wished to determine whether such differences, if any, were associated with age- and sex-related differences in mortality.

## Patients and Methods

### Setting and Design

This population-based follow-up study was conducted using data from the entire Danish population (~5.5 million people). The Danish National Health Service provides tax-supported health care to all Danish residents, including free access to general practitioners and hospitals, and also refunds a variable proportion of prescription medication costs.

The Danish Civil Registration System has maintained electronic records of changes in the vital status of all citizens since 1968 [17]. Each record carries a unique 10-digit civil registration

number that is assigned to every Danish citizen and is used in all Danish registries. For this study, we obtained information on mortality after discharge from the Civil Registration System.

### Study Population

We identified all patients admitted with acute stroke who were registered in the Danish National Indicator Project (DNIP) from January 1, 2003, to June 30, 2006 ( $n = 36,075$ ). DNIP is a nationwide initiative to monitor and improve the quality of care for specific diseases, including stroke [18]. This is accomplished by monitoring fulfillment of quality criteria related to the structure, process and outcome of health care. Participation in the project is mandatory for all hospital departments in Denmark that treat patients with acute stroke. All adult patients ( $\geq 18$  years) admitted to Danish hospitals with acute stroke according to WHO criteria are eligible for inclusion in the DNIP (i.e. patients who rapidly develop clinical signs of focal or global disturbance of cerebral function lasting  $>24$  h or until death with no apparent non-vascular cause [19]). We excluded 4,870 patients who died in hospital or within 30 days after hospital discharge. We also excluded 2,548 patients with hemorrhagic stroke and 23 with missing information regarding admission and/or discharge dates. We included only the first stroke event registered during the study period, and we restricted the study population to patients residing in Denmark and who were therefore available for follow-up. Data from a total of 28,634 patients were available for further analysis (fig. 1).

### Medical Prophylaxis

Data for prescriptions filled after discharge was obtained by linkage with the Medical Register of the Danish Medicine Agency. The register contains data from 1995 onward for all prescription drugs dispensed at all Danish pharmacies, including the type of drug and the date it was dispensed. We traced all prescriptions for antiplatelets, oral anticoagulants, ACE inhibitors, ATII antagonists,  $\beta$ -blockers, calcium blockers, thiazide diuretics and statins that were filled by stroke patients up to 18 months after hospital discharge. In Denmark, these drugs are available by prescription only, except for low-dose acetylsalicylic acid (ASA). However, low-dose ASA is generally prescribed by physicians rather than bought over the counter since chronic users and pensioners can be reimbursed for prescription drugs. Antiplatelets

included low-dose ASA, clopidogrel and dipyridamole. Drug use was defined as filled prescriptions and assessed for two time windows: 0–6 and 12–18 months after hospital discharge.

#### *Patient Characteristics*

At the time of hospital admission, the following data were collected: sex, marital status (living with partner, family or friend, or living alone), type of residence (own home, nursing home or other type of institution), Scandinavian Stroke Scale score (a measure of stroke severity [20, 21]), history of stroke and myocardial infarction, previous and/or current atrial fibrillation, hypertension, diabetes mellitus or intermittent claudication, smoking habits (smoker, ex-smoker or never) and alcohol intake ( $\leq 14/21$ ,  $>14/21$  drinks per week for women and men, respectively). Information on the quality of in-hospital care during the acute phase, which has been linked with survival [22], was obtained from the DNIP and included data on fulfillment of seven quality-of-care criteria. The criteria were as follows: early admission to a specialized stroke unit, early administration of antiplatelet or anticoagulant therapy, early examination with CT/MRI, early assessment by a physiotherapist and an occupational therapist, and assessment of nutritional risks. We computed the percentage of indicators fulfilled for each patient as a measure of the quality of in-hospital stroke care. We also computed the Charlson comorbidity index score for each patient based on all discharge diagnoses recorded before hospitalization for stroke. Data on previous hospitalizations were obtained from the National Registry of Patients, which contains data on all discharges from all non-psychiatric hospitals in Denmark since 1977 [23]. The Charlson comorbidity index covers 19 major disease categories and has been reported to be useful for patients with stroke [24–26]. We defined three levels of comorbidity: 0 comorbidities ('none'), 1–2 comorbidities ('moderate') and  $>2$  comorbidities ('high'). Former stroke, myocardial infarction and diabetes were excluded from the index and were instead included as individual covariates due to the well-established prognostic role of these conditions.

Information on the socioeconomic status the year prior to hospital admission was obtained from the Integrated Database for Labor Market Research. The socioeconomic status classification was based on information on the annual income and source of income for each person and was collected from tax returns and other public registries [27].

More detailed data, including the modified Rankin score before admission (which reflects a patient's functional ability before the stroke [28]) and discharge residence (rehabilitation ward, own residence, care residence or other type of residence), were available for patients admitted to hospitals in the areas of Copenhagen and Aarhus ( $n = 6,501$ ).

#### *Statistical Analysis*

We first assessed the use of medical prophylaxis by computing the proportion of patients who filled at least one prescription for a drug in the specified drug classes 0–6 and 12–18 months after hospital discharge. We defined continued use of medical prophylactic treatment as the proportion of patients who were alive 18 months after discharge and who had filled at least one prescription in both time windows.

Second, we used logistic regression analysis to perform crude and adjusted comparisons across age and sex groups using men  $\leq 65$  years as a reference. Comparisons of oral anticoagulant ther-

apy included only patients with atrial fibrillation and without registered contraindications for anticoagulant therapy during hospital admission.

Third, we computed age- and sex-specific mortality rates in two follow-up periods: from 30 days to 6 months (henceforth referred to as 1–6 months) and 12–18 months. Follow-up started on day 30 after hospital discharge and ended on the date of death, emigration or at the end of the specific follow-up period, whichever came first. We used Cox proportional hazards regression to obtain crude and adjusted age- and sex-specific mortality rate ratios (MRR) in the two periods. We adjusted for differences in patient characteristics, quality of in-hospital care and use of medical prophylaxis after discharge. Likelihood ratio tests were used to compare the fit of Cox models with and without variables with the use of secondary prophylaxis.

Finally, we performed sub-analyses of patients from two regions: Copenhagen and Aarhus County. In these analyses, we also adjusted for modified Rankin scores before admission and type of discharge residence in order to assess whether these covariates had an impact on our results. All analyses that were adjusted for patient prognostic factors were performed both with and without patients who had missing data. We analyzed the data using STATA version 10.1 (StataCorp).

## **Results**

Table 1 shows the characteristics of the 28,634 patients according to age. Increasing age was associated with a more adverse prognostic profile, including more severe stroke and lower-quality in-hospital stroke care. Female sex was associated with increasing age, atrial fibrillation, hypertension, increased stroke severity and care home residency; in addition, more women than men lived alone (data not shown). In contrast, male sex was associated with diabetes, myocardial infarction, previous stroke, intermittent claudication, high alcohol intake and daily smoking (data not shown).

#### *Use of Medical Prophylaxis*

Figure 2 shows the proportion of patients receiving medical prophylaxis by age and sex, and table 2 displays the corresponding adjusted odds ratios (ORs). Increasing age was associated with a lower proportion of patients receiving antiplatelet therapy, anticoagulant therapy, statins and combination therapy both 0–6 and 12–18 months after discharge. In contrast, we identified no overall systematic sex-related differences in prophylaxis after hospital discharge. However, between 0 and 6 months, women  $\leq 65$  years were less likely to receive ACE inhibitors/ATII antagonists (adjusted OR 0.74, 95% confidence interval, CI: 0.67–0.83), but more likely to receive thiazides (adjusted OR 1.13, 95% CI: 1.01–1.28) compared

**Table 1.** Characteristics of the 28,634 patients admitted with ischemic stroke in Denmark, 2003–2006, stratified by age

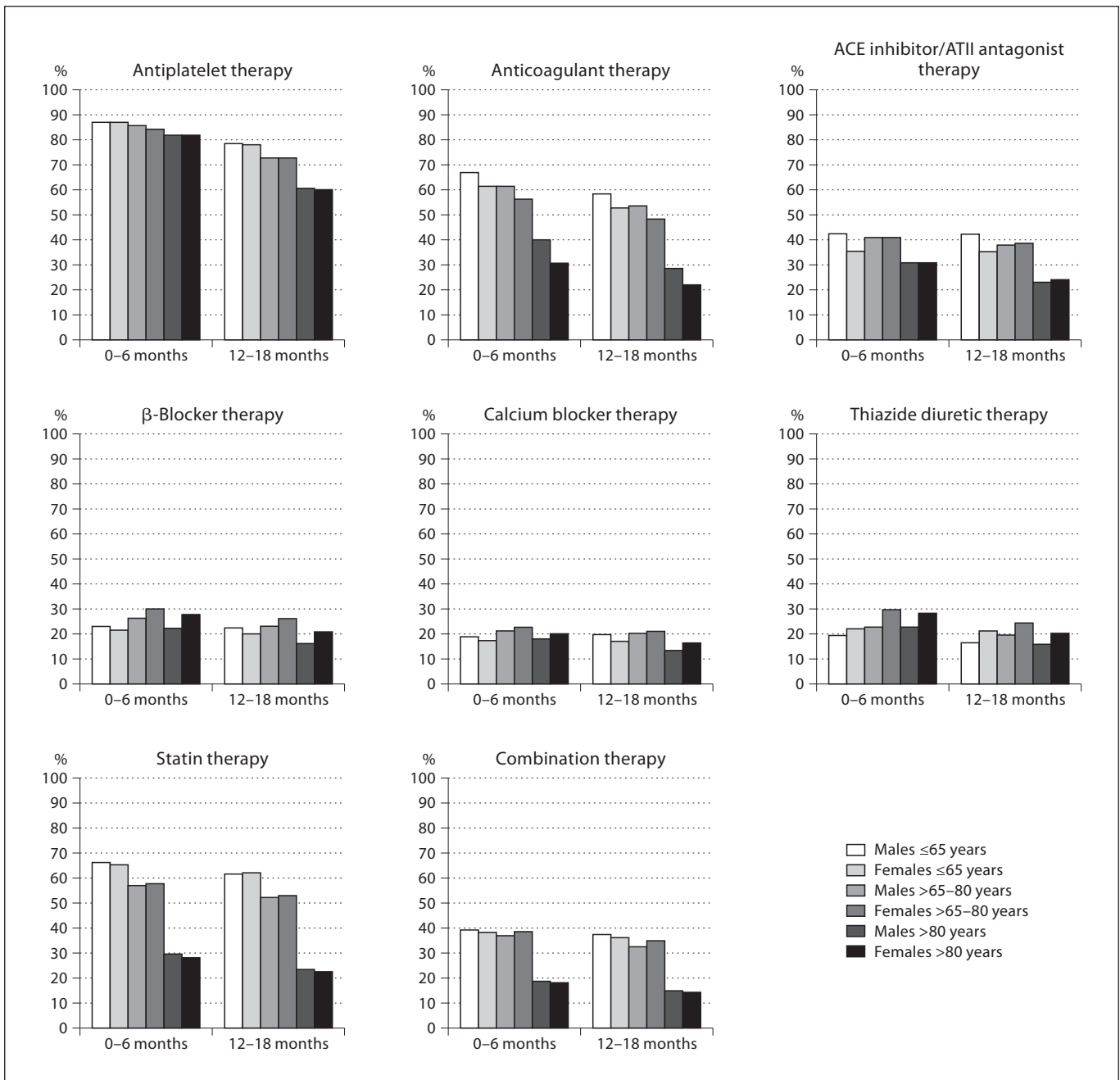
	≤65 years (n = 9,019)	>65–80 years (n = 12,173)	>80 years (n = 7,442)
<i>Sex</i>			
Male	5,751 (63.8%)	6,643 (54.6%)	2,785 (37.4%)
Female	3,268 (36.2%)	5,530 (45.4%)	4,657 (62.6%)
<i>Comorbidity</i>			
<i>Charlson index</i>			
None (0 point)	5,194 (57.6%)	5,160 (42.4%)	2,943 (39.5%)
Low (1–2 points)	2,906 (32.2%)	4,857 (39.9%)	3,167 (42.6%)
High (>2 points)	919 (10.2%)	2,156 (17.7%)	1,332 (17.9%)
<i>Diabetes mellitus</i>			
Yes	1,205 (13.4%)	1,782 (14.6%)	811 (10.9%)
No	7,322 (81.2%)	9,654 (79.3%)	6,097 (81.9%)
Undisclosed	426 (4.7%)	644 (5.3%)	477 (6.4%)
<i>Atrial fibrillation</i>			
Yes	477 (5.3%)	1,785 (14.7%)	1,915 (25.7%)
No	7,980 (88.5%)	9,528 (78.3%)	4,928 (66.2%)
Undisclosed	490 (4.7%)	760 (6.2%)	544 (7.3%)
<i>Myocardial infarction</i>			
Yes	569 (6.3%)	1,334 (11.0%)	725 (9.7%)
No	7,906 (87.7%)	9,926 (81.5%)	5,975 (80.3%)
Undisclosed	475 (5.3%)	817 (6.7%)	679 (9.1%)
<i>Hypertension</i>			
Yes	3,570 (39.6%)	5,825 (47.9%)	3,255 (43.7%)
No	4,847 (53.7%)	5,384 (44.2%)	3,403 (45.7%)
Undisclosed	538 (6.0%)	879 (7.2%)	729 (9.8%)
<i>Previous stroke</i>			
Yes	1,563 (17.3%)	2,878 (23.6%)	1,738 (23.4%)
No	6,958 (77.1%)	8,521 (70.0%)	5,084 (68.3%)
Undisclosed	425 (4.7%)	685 (5.6%)	566 (7.6%)
<i>Intermittent claudication</i>			
Yes	270 (3.0%)	584 (4.8%)	236 (3.2%)
No	7,853 (87.1%)	9,939 (81.6%)	5,837 (78.4%)
Undisclosed	809 (9.0%)	1,528 (12.6%)	1,300 (17.5%)
<i>Stroke severity score</i>			
Very severe (0–14 points)	344 (3.8%)	575 (4.7%)	475 (6.4%)
Severe (15–29 points)	480 (5.3%)	851 (7.0%)	742 (10.0%)
Moderate (30–44 points)	1,052 (11.7%)	2,077 (17.1%)	1,765 (23.7%)
Mild (45–58 points)	5,912 (65.6%)	7,003 (57.5%)	3,312 (44.5%)
<i>Smoking</i>			
Daily	4,796 (53.2%)	4,188 (34.4%)	1,112 (14.9%)
Occasionally	156 (1.7%)	212 (1.7%)	97 (1.3%)
Ex-smoker (>6 months)	1,204 (13.3%)	2,620 (21.5%)	1,401 (18.8%)
Never smoked	1,976 (21.9%)	3,380 (27.8%)	2,976 (40.0%)
Undisclosed	795 (8.8%)	1,635 (13.4%)	1,792 (24.1%)
<i>Alcohol</i>			
14/21 drinks/week or fewer	6,829 (75.7%)	9,665 (79.4%)	5,775 (77.6%)
More than 14/21 drinks/week	1,183 (13.1%)	697 (5.7%)	112 (1.5%)
Undisclosed	910 (10.1%)	1,659 (13.6%)	1,495 (20.1%)

**Table 1** (continued)

	≤65 years (n = 9,019)	>65–80 years (n = 12,173)	>80 years (n = 7,442)
<i>Residence type</i>			
Own residence	8,051 (89.3%)	10,721 (88.1%)	5,886 (79.1%)
Care home	118 (1.3%)	444 (3.6%)	931 (12.5%)
Other	200 (2.2%)	190 (1.6%)	166 (2.2%)
Undisclosed	566 (6.3%)	693 (5.7%)	395 (5.3%)
<i>Civil status</i>			
Co-habitant	6,143 (68.1%)	6,746 (55.4%)	2,191 (29.4%)
Lives alone	2,326 (25.8%)	4,652 (38.2%)	4,622 (62.1%)
Other	118 (1.3%)	157 (1.3%)	283 (3.8%)
Undisclosed	361 (4.00%)	500 (4.1%)	291 (3.9%)
<i>Percentage of fulfilled indicators</i>			
<50%	1,676 (18.6%)	2,667 (21.9%)	1,939 (26.1%)
50–99%	4,206 (46.6%)	5,768 (47.4%)	3,573 (48.0%)
100%	3,114 (34.5%)	3,697 (30.4%)	1,903 (25.6%)
<i>Socioeconomic status</i>			
Self-employed with employees	181 (2.0%)	36 (0.3%)	2 (0.0%)
Self-employed without employees	332 (3.7%)	190 (1.6%)	39 (0.5%)
Top manager	139 (1.5%)	8 (0.1%)	1 (0.0%)
Salaried employee, upper level	436 (4.8%)	27 (0.2%)	0
Salaried employee, intermediate level	614 (6.8%)	18 (0.1%)	0
Salaried employee, basic level	1,581 (17.5%)	48 (0.4%)	1 (0.0%)
Salaried employee, other	509 (5.6%)	29 (0.2%)	0
Employee, not further specified	707 (7.8%)	108 (0.9%)	18 (0.2%)
Assisting spouse	24 (0.3%)	11 (0.1%)	0
Unemployed	413 (4.6%)	4 (0.0%)	0
Disability supplement	2,218 (24.6%)	307 (2.5%)	0
Old-age pensioners	43 (0.5%)	10,629 (87.3%)	7,373 (99.1%)
Early retirement benefits	1,112 (12.3%)	695 (5.7%)	1 (0.0%)
Other economically inactive persons	264 (2.9%)	4 (0.0%)	0
Other	416 (4.6%)	34 (0.3%)	1 (0.0%)
<i>Rankin score before admission<sup>1</sup></i>			
0	1,182 (60.3%)	1,246 (46.2%)	547 (29.6%)
1	214 (10.9%)	448 (16.6%)	315 (17.1%)
2	129 (6.6%)	245 (9.1%)	242 (13.1%)
3	50 (2.5%)	142 (5.3%)	189 (10.2%)
4	32 (1.6%)	113 (4.2%)	146 (7.9%)
5	3 (0.2%)	14 (0.5%)	16 (0.9%)
Undisclosed	262 (13.3%)	362 (13.4%)	312 (16.9%)
<i>Discharge residence<sup>1</sup></i>			
Rehabilitation ward	46 (2.3%)	86 (3.2%)	61 (3.3%)
Own residence	1,612 (82.2%)	2,004 (74.4%)	1,068 (57.9%)
Care residence	65 (3.3%)	220 (8.2%)	452 (24.5%)
Other	88 (4.5%)	162 (6.0%)	129 (7.0%)
Undisclosed	64 (3.2%)	130 (4.8%)	68 (3.7%)

All p values were below 0.0001 for differences in age group distribution within each of the patient characteristics.

<sup>1</sup> Information only available for the Copenhagen area and Aarhus County: ≤65 (n = 1,961), >65–80 (n = 2,694), >80 (n = 1,846).



**Fig. 2.** Proportions of patients receiving medical prophylaxis after hospital discharge by age and sex.

with men of the same age. The more widespread use of thiazides among women was seen in all age groups in both time windows.

Continued use of medical prophylaxis 12–18 months after discharge ranged from 66.1% (thiazide therapy

among males ≤65 years) to 91.9% (antiplatelet therapy among males >65–80 years). There were no substantial differences in continued use across age groups for most drug groups. However, for anticoagulant therapy, ACE inhibitors/ATII antagonists, statins and combination thera-

**Table 2.** Adjusted ORs for medical prophylaxis after hospital discharge by age and sex among patients with ischemic stroke

	Adjusted ORs (95% CIs)			Adjusted ORs (95% CIs)	
	0–6 months (n = 24,179)	12–18 months (n = 21,017)		0–6 months (n = 24,179)	12–18 months (n = 21,017)
<i>Antiplatelets</i>			<i>Calcium blockers</i>		
Males ≤65 years	1.00	1.00	Males ≤65 years	1.00	1.00
Females ≤65 years	1.10 (0.95–1.29)	1.00 (0.88–1.13)	Females ≤65 years	0.91 (0.80–1.04)	0.85 (0.75–0.97)
Males >65–80 years	1.01 (0.83–1.23)	1.08 (0.90–1.30)	Males >65–80 years	0.97 (0.82–1.15)	0.99 (0.84–1.17)
Females >65–80 years	1.02 (0.83–1.26)	1.03 (0.85–1.26)	Females >65–80 years	1.03 (0.86–1.23)	1.06 (0.89–1.27)
Males >80 years	1.07 (0.84–1.35)	1.14 (0.91–1.43)	Males >80 years	0.81 (0.66–0.99)	0.78 (0.63–0.96)
Females >80 years	1.19 (0.94–1.49)	1.16 (0.93–1.44)	Females >80 years	0.99 (0.81–1.20)	1.02 (0.84–1.25)
<i>Oral anticoagulants<sup>1</sup></i>			<i>Thiazide diuretics</i>		
	n = 3,537	n = 2,718	Males ≤65 years	1.00	1.00
Males ≤65 years	1.00	1.00	Females ≤65 years	1.13 (1.01–1.28)	1.36 (1.20–1.53)
Females ≤65 years	1.05 (0.56–1.96)	0.90 (0.51–1.59)	Males >65–80 years	0.98 (0.84–1.15)	1.12 (0.94–1.32)
Males >65–80 years	0.77 (0.42–1.42)	1.07 (0.59–1.95)	Females >65–80 years	1.23 (1.04–1.46)	1.39 (1.17–1.67)
Females >65–80 years	0.67 (0.36–1.24)	0.74 (0.40–1.37)	Males >80 years	1.06 (0.88–1.28)	1.15 (0.94–1.42)
Males >80 years	0.42 (0.22–0.79)	0.46 (0.24–0.88)	Females >80 years	1.27 (1.06–1.53)	1.43 (1.18–1.75)
Females >80 years	0.45 (0.24–0.85)	0.56 (0.29–1.06)	<i>Statins</i>		
<i>ACE inhibitors/ATII antagonists</i>			Males ≤65 years	1.00	1.00
Males ≤65 years	1.00	1.00	Females ≤65 years	1.00 (0.90–1.11)	1.02 (0.92–1.14)
Females ≤65 years	0.74 (0.67–0.83)	0.75 (0.68–0.84)	Males >65–80 years	0.96 (0.83–1.10)	1.00 (0.86–1.16)
Males >65–80 years	0.87 (0.75–1.01)	0.88 (0.76–1.02)	Females >65–80 years	1.23 (1.05–1.43)	1.24 (1.06–1.45)
Females >65–80 years	0.87 (0.75–1.02)	0.89 (0.76–1.04)	Males >80 years	0.37 (0.31–0.44)	0.39 (0.32–0.46)
Males >80 years	0.63 (0.53–0.76)	0.57 (0.47–0.69)	Females >80 years	0.46 (0.38–0.54)	0.47 (0.39–0.56)
Females >80 years	0.62 (0.52–0.74)	0.58 (0.49–0.70)	<i>Combination therapy (antiplatelet, antihypertensive<sup>2</sup> + statin)</i>		
<i>β-Blockers</i>			Males ≤65 years	1.00	1.00
Males ≤65 years	1.00	1.00	Females ≤65 years	1.00 (0.90–1.11)	0.99 (0.89–1.10)
Females ≤65 years	0.97 (0.86–1.10)	0.94 (0.84–1.07)	Males >65–80 years	0.93 (0.81–1.08)	0.92 (0.79–1.06)
Males >65–80 years	0.88 (0.75–1.03)	0.87 (0.73–1.02)	Females >65–80 years	1.18 (1.01–1.38)	1.19 (1.02–1.40)
Females >65–80 years	1.10 (0.93–1.30)	1.07 (0.90–1.27)	Males >80 years	0.45 (0.38–0.54)	0.44 (0.37–0.54)
Males >80 years	0.61 (0.50–0.74)	0.62 (0.50–0.76)	Females >80 years	0.52 (0.43–0.62)	0.52 (0.43–0.62)
Females >80 years	0.88 (0.73–1.06)	0.91 (0.75–1.11)			

ORs were adjusted for the following: stroke severity, Charlson index, diabetes mellitus, atrial fibrillation, myocardial infarction, hypertension, former stroke, intermittent claudication, percentage of fulfilled indicators, smoking status, alcohol intake, type of residence, socioeconomic status and civil status.

<sup>1</sup> Only includes patients with atrial fibrillation and no contraindications for anticoagulant therapy during hospital admission.

<sup>2</sup> Antihypertensive: ACE inhibitor, ATII antagonist, β-blocker, calcium blocker or thiazide diuretic.

py, a decrease in continued use was observed with increasing age. No systematic sex differences in continued use of medical prophylaxis were observed (data not shown).

A total of 851 patients (3.0%) received no secondary medical prophylaxis after discharge.

The sub-analysis of patients from the Copenhagen and Aarhus areas showed exactly the same results as the original analysis, indicating that differences in modified Rankin scores before admission and in discharge residence type did not explain our findings.

Results were not dependent on whether patients with missing data on prognostic factors were included in the analysis (data not shown).

#### Age- and Sex-Related Differences in Mortality

Age- and sex-specific cumulative mortality rates and MRRs for both time periods (1–6 and 12–18 months) are presented in table 3. The range for cumulative mortality was 1.8–12.2% for the first period and 1.4–10.7% for the second period, respectively, for men in the three age

**Table 3.** Cumulative mortality rates and MRRs 1–6 and 12–18 months after hospital discharge among patients with ischemic stroke

Age years	Sex	1–6 months				12–18 months			
		proportion of patients who died, n (%)	unadjusted MRR (95% CI) (n = 28,632)	adjusted MRR <sup>1</sup> (95% CI) (n = 24,179)	fully adjusted MRR <sup>2</sup> (95% CI) (n = 24,179)	proportion of patients who died, n (%)	unadjusted MRR (95% CI) (n = 25,532)	adjusted MRR <sup>1</sup> (95% CI) (n = 21,662)	fully adjusted MRR <sup>2</sup> (95% CI) (n = 21,662)
All	males	818/15,179 (5.39)	1.00 (reference)	1.00 (reference)	1.00 (reference)	553/13,661 (4.05)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	females	957/13,453 (7.11)	1.33 (1.21–1.46)	0.85 (0.76–0.95)	0.89 (0.80–1.00)	564/11,871 (4.75)	1.18 (1.05–1.33)	0.90 (0.78–1.03)	0.95 (0.82–1.10)
≤65	males	101/5,751 (1.76)	1.00 (reference)	1.00 (reference)	1.00 (reference)	78/5,537 (1.4)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	females	46/3,267 (1.41)	0.80 (0.56–1.13)	0.67 (0.44–1.02)	0.67 (0.44–1.02)	40/3,170 (1.3)	0.90 (0.61–1.31)	0.81 (0.53–1.24)	0.87 (0.57–1.33)
>65–80	males	376/6,643 (5.66)	3.28 (2.63–4.08)	1.84 (1.25–2.72)	1.85 (1.25–2.73)	245/5,967 (4.1)	2.96 (0.30–3.82)	1.68 (1.08–2.63)	1.80 (1.15–2.82)
	females	294/5,530 (5.32)	3.08 (2.46–3.86)	1.50 (1.00–2.25)	1.58 (1.05–2.37)	183/5,044 (3.7)	2.60 (2.00–3.39)	1.50 (0.94–2.38)	1.68 (1.06–2.68)
>80	males	341/2,785 (12.24)	7.39 (5.92–9.22)	3.40 (2.25–5.13)	2.86 (1.89–4.32)	230/2,157 (10.7)	7.91 (6.12–10.23)	4.01 (2.49–6.46)	3.37 (2.09–5.42)
	females	617/4,656 (13.25)	8.02 (6.50–9.90)	2.87 (1.90–4.34)	2.63 (1.74–3.97)	341/3,657 (9.3)	6.91 (5.40–8.83)	3.42 (2.12–5.51)	3.14 (1.95–5.07)

<sup>1</sup> Adjusted for patient characteristics (stroke severity, Charlson index, diabetes mellitus, atrial fibrillation, myocardial infarction, hypertension, former stroke, intermittent claudication, percentage of fulfilled indicators, smoking, alcohol, type of residence, socioeconomic status and civil status).

<sup>2</sup> Additionally adjusted for use of antiplatelets, ACE inhibitors/ATII antagonists,  $\beta$ -blockers, calcium blockers, thiazide diuretics and statins.

groups. The corresponding mortality for women ranged from 1.4 to 13.3% within the first 6 months and from 1.3 to 9.3% for the 12- to 18-month period. As expected, we found a reduction in MRRs after adjustment for patient characteristics, including clinical, sociodemographic and socioeconomic characteristics. Further adjustment for use of secondary medical prophylaxis was associated with even lower MRRs (likelihood ratio test:  $p < 0.001$ ). A similar pattern was found in our analysis of patients from the Copenhagen and Aarhus County areas for the later time window; this pattern was independent of whether patients with missing prognostic data were included in the analysis (data not shown).

## Discussion

In this nationwide follow-up study, we found an inverse association between age and use of medical prophylaxis following an ischemic stroke for most types of cardiovascular drugs. For some drugs, increasing age was also associated with a lower rate of continued drug use. In contrast, we found no indication of any sex-related dif-

ferences in prophylaxis. The age-related differences in the use of secondary prophylaxis were associated with the higher mortality observed among elderly patients.

### Strengths and Limitations

The main strength of this study is its prospective, population-based design with complete long-term follow-up and low risk of selection and information bias. Our analyses were based on a large cohort, with detailed information on all individuals in terms of clinical and sociodemographic characteristics, in-hospital stroke treatment and use of medical prophylaxis after hospital discharge; this limited the risk of chance findings and confounding.

The use of data collected in a non-standardized setting during routine clinical work is a limitation that potentially affects the accuracy of the collected data. However, we note that participation in the DNIP is obligatory for all departments treating patients with acute stroke in Denmark, and great effort is made to ensure the validity of the DNIP [18]. Specifically, a regular structured audit is conducted nationally, regionally and locally that includes validation of the completeness of patient registration against county hospital discharge registries. Fur-

thermore, any misclassification of data in DNIP is unlikely to depend on age and sex.

We were not able to determine from our data whether patients who did not use secondary prophylaxis had not received a prescription or whether the patient had failed to fill the prescription at the pharmacy. We used prescriptions as a proxy measure of drug use, since we only included data on prescriptions that had been filled and because the patients were only partly reimbursed (i.e. patients who pick up drugs at the pharmacy and pay for them partly out of their own pocket were assumed to be more likely to actually use the drugs). Further, in our analyses on continued use, we applied a rather conservative approach in which all patients included were alive 18 months after hospital discharge and had filled at least one prescription during the periods of interest. This method most likely provided us with 'best-case' estimates. Thus, we may have overestimated the true proportion of patients who continued to use medical prophylaxis in our study population.

Although we adjusted for a wide range of covariates, we cannot exclude the possibility that our results were influenced by residual confounding due to the use of crude variables (e.g. data on levels of hypertension were not available) or due to unaccounted confounding from factors that were not included in the analyses (e.g. mental function). The prevalence of patients with missing data for the prognostic factors ranged between 5 and 30%. Although missing data are a reason for concern, it seems unlikely that this had any substantial influence on our findings, which remained virtually unchanged regardless of whether patients with missing data were included in the analyses.

#### *Comparison with Other Studies*

Only a few studies have examined the use of secondary prophylaxis among patients with ischemic stroke. However, in accordance with our findings, the existing studies have indicated that secondary prophylaxis has not been sufficiently implemented. Lalouschek et al. [29] examined in-hospital use of statins among 1,743 Austrian patients admitted with ischemic stroke between 1998 and 2001 and found that overall, 23% of the patients and 32% of those with clinically relevant atherosclerosis and cholesterol levels >200 mg/dl received statin therapy at discharge. The same study found that patients aged 75–84 and 85+ had ORs of 0.5 (95% CI: 0.3–0.9) and 0.2 (95% CI: 0.1–0.3), respectively, for receiving statin treatment compared to younger patients (<55 years). Ovbiagele et al. [30] found similar patterns for overall statin use dur-

ing hospitalization in a study of 2,894 patients with ischemic stroke admitted 1996–2003 to medical centers in the United States and Canada. Almost half of the patients who were considered to be at high vascular risk were not prescribed a statin, even though they had LDL-C concentrations above the target value for treatment initiation. In the present study, between 28 and 66% of patients had received statin treatment up to 6 months after discharge. In agreement with the study by Lalouschek et al. [29], we found that elderly people were less likely to receive statins.

Underuse of oral anticoagulation therapy among ischemic stroke patients has been found consistently [31]. We reported previously that fewer than 70% of eligible Danish ischemic stroke patients receive oral anticoagulants in the early phase after stroke: this percentage was as low as 44% for patients >80 years [5]. The findings from the present study illustrate that underuse is not limited to the early phase of stroke when there might be uncertainty about when best to initiate treatment. Instead, there appears to be particular difficulties in terms of implementing treatment in eligible elderly patients.

The reasons for lower prophylaxis use among elderly patients are not clear. Making decisions about the use of secondary prophylaxis in elderly patients includes considerations about the impact of comorbidities, the ability to comply with treatment and the risks of adverse effects. Thus, there may be valid clinical arguments for treating individual elderly patients differently than their younger counterparts. Although clinical guidelines recommend lifelong medical prophylaxis based on findings from randomized controlled trials, the effect of secondary medical prophylaxis among the very elderly patients has been debated [32, 33]. This is in part due to the relatively sparse data available from randomized controlled trials in addition to some particular age-related complicating issues such as comorbidity and dementia. Consequently, it could be argued that a lower proportion of the very elderly are expected to be eligible for secondary medical prophylaxis. In the present study, we tried to account for this important issue by controlling for differences in comorbidity, stroke severity and dependency before admission in the multivariable analyses and by restricting our analyses on use of oral anticoagulants to patients considered eligible for the treatment during hospitalization. Still the observed age-related differences in use of secondary medical prophylaxis remained substantial. There are still relatively few data regarding the efficacy and effectiveness of secondary prophylaxis for elderly patients, and some of these data were not available at the time this study was conducted. For example, results of the Hyper-

tension in the Very Elderly Trial were first published in 2008 [34]. The present study period therefore encompasses a time interval in which the indications for use of secondary medical prophylaxis were less specific (e.g. treatment with statins after hospital discharge was for many patients probably prescribed due to coexisting coronary heart disease rather than due to the ischemic stroke). However, no guidelines recommended that use of statins or other types of secondary medical prophylaxis was restricted to younger patients.

Other studies have investigated potential sex-related differences in the treatment of stroke patients [6–9, 13, 35]. However, these studies mainly investigated in-hospital treatment and quality of care. In agreement with the studies that found no sex-related differences in acute stroke care [13, 35], we found no systematic differences between men and women in medical prophylaxis use after discharge.

In conclusion, we found that in a single-provider, tax-financed health care system, elderly patients were substantially less likely to receive secondary prophylaxis after hospital discharge following an ischemic stroke compared with younger patients. Continued drug use also appeared to be lower among elderly patients. These age-related differences in use of secondary prophylaxis were associated with a higher mortality among the elderly patients. In contrast, we found no overall systematic sex-related differences in the use of secondary prophylaxis. Continuous efforts are warranted to ensure optimal secondary medical prophylaxis among patients with stroke regardless of their age.

### Disclosure Statement

None.

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