Implementation of clinical guidelines regarding acute treatment and secondary medical prophylaxis among patients with acute stroke in Denmark

PhD thesis

Kaare Haurvig Palnum

Faculty of Health Sciences

Aarhus University

Department of Clinical Epidemiology, Aarhus University Hospital

Supervisors

Søren Paaske Johnsen, Associate professor, PhD, MD

Department of Clinical Epidemiology

Aarhus University Hospital, Denmark

Grethe Andersen, Associate professor, DMSc

Department of Neurology

Aarhus University Hospital, Denmark

Evaluation Committee

Birgitta Stegmayr, Professor, MD

Unit of Epidemiology

National Board of Health and Welfare, Sweden

Gudrun Boysen, Professor, DMSc

Department of Neurology

Bispebjerg Hospital, Denmark

Steen E. Husted, Associate professor, DMSc

Department of Medical Cardiology

Aarhus University Hospital, Denmark

This thesis is dedicated to

Niels Lyhne Dyre Palnum

January 20th 1942 – November 14th 2009

A beloved father who sadly experienced the hardships and consequences of stroke first hand.

Preface

In 2005, I had my first meeting with Søren Paaske Johnsen at the Department of Clinical Epidemiology with the purpose of discussing a potential research year project. Little did I know that this meeting would essentially keep me busy for the next five years!

A lot has happened during these past five years, both personally and professionally. However, one thing is for certain; this thesis would not have been possible without the help, guidance, and support of a lot of wonderful people. First of all, I would like to thank my supervisors: Søren Paaske Johnsen, for patiently teaching me to safely navigate the intricacies of clinical epidemiology, for his enthusiasm, patience, humor, and for his unfaltering dedication to both the project and to me; Grethe Andersen for her professional advice and for her willingness to share her vast experience and expertise in clinical stroke practices. If I had to do it all again, I do not believe I could find better counseling and guidance than that given me by these people.

Also, I would like to thank Frank Mehnert for expert statistical support, construction of datasets, and for being patient with me every time I needed a new dataset constructed with "just a few extra variables". I would also like to thank my co-authors, Palle Petersen, Annette Ingeman, Birgitte Krog, Paul Bartels, and Henrik Toft Sørensen for their great advice and input in these studies.

I am deeply grateful to all of my friends and colleagues at the Department of Clinical Epidemiology for creating a warm and professional work environment that allowed fruitful discussions and contemplation, as well as laughs and good times.

Additionally, I would like to thank my colleagues at the stroke unit in the Regional Hospital of Randers and Grenaa for giving me the opportunity of working regularly with "real life" stroke patients for the past two years and always reminding me that behind the patient identification numbers in my datasets were real people with faces, names, and feelings. Furthermore, I extend my sincere gratitude to my friend and colleague, Ole Davidsen, for kindling my interest in research in the beginning.

Finally, I give my dearest thanks to my wonderful wife Lone, for her love, unwavering support, for always believing in me, even when I did not believe, and for soon delivering our firstborn son.

This PhD thesis is based on the following papers:

I. Palnum KD, Petersen P, Sørensen HT, Ingeman A, Mainz J, Bartels P, Johnsen SP. Older patients with acute stroke in Denmark: quality of care and short-term mortality. A nationwide follow-up study. Age and Ageing 2008; 37: 90–95.

II. Palnum KD, Andersen G, Ingeman A, Krog BR, Bartels P, Johnsen SP. Sex-related differences in quality of care and short-term mortality among patients with ischemic stroke in Denmark. A nationwide follow-up study. Stroke. 2009;40:1134-1139.

III. Palnum KH, Mehnert F, Andersen G, Ingeman A, Krog BR, Bartels P, Johnsen SP. Medical prophylaxis following hospitalization with ischemic stroke: age- and sex-related differences and relation to mortality. Submitted to Cerebrovascular Diseases 2010.

IV. Palnum KH, Mehnert F, Andersen G, Ingeman A, Krog BR, Bartels P, Johnsen SP. Effectiveness of secondary medical prophylaxis following hospitalization with ischemic stroke. In preparation.

Contents

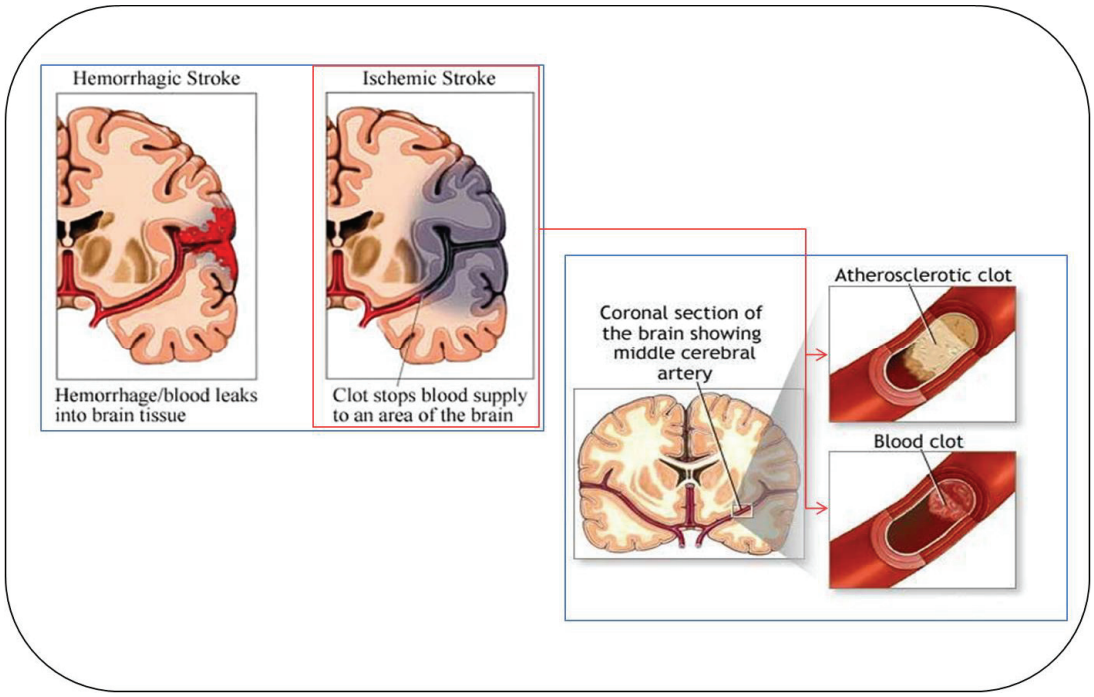
1. Introduction

1.1 Epidemiology of stroke

Stroke is a significant public health problem. According to World Health Organization (WHO) estimates, 15 million people experience a stroke each year, and, as a result, 5 million become permanently disabled.[1-3] In 2002, the WHO estimated that 5.5 million people died from stroke worldwide; this corresponded to 11.0% and 8.4% of all deaths among women and men, respectively.[1, 2] Every year, approximately 12 000 to 13 000 Danes experience a stroke. Depending on the type of stroke, approximately 20 to 30% of patients are predicted to die in the acute phase of a stroke or within the first year after the stroke. This high incidence and case-fatality had made stroke the third most frequent cause of death in the Western world. Furthermore, many that survive a stroke must adjust to a disabling condition, like paralysis, aphasia, dementia, epilepsy, depression, or fall trauma. In Denmark, 30 000 to 40 000 survivors of stroke are currently living with consequential disabilities; thus, stroke is the most important cause of permanent disability among adults in Denmark. The direct costs of stroke were estimated to be 2.7 billion DKR in 2001, which was equivalent to approximately 4% of the total hospital expenses in Denmark. Therefore, stroke has demanded more resources than any other disease in the Danish heath care system.[4] When all stroke-related expenses were taken into account, including pension, homecare, assistive technology, medicine etc., the cost per patient was estimated at approximately 160 000 DKR; this amounted to a total cost of 7 billion DKR per year for all stroke patients in 2001.[4, 5]

A recent systematic review based on 98 papers from 59 studies published during the last 40 years from around the world estimated that first-ever strokes occurred at a mean age of 68.6 years among men and 72.9 years among women.[6] The incidence rate of stroke was 33% higher and the prevalence was 41% higher among males compared to females, with large variations between age groups and between populations. In contrast, stroke tended to be more severe among women than among men; the 1-month case fatality was 24.7% among women compared to 19.7% among men.[6] However, these sex-related differences also included an age-related effect, because women were generally older than men when they experienced a first-ever stroke.

Figure 1: Hemorrhagic and ischemic stroke



1.2 Definition of stroke

The WHO defined stroke as the rapid development of clinical signs of a focal or global disturbance of cerebral function that lasts more than 24 hours or until death, with no apparent nonvascular cause.[7] There are two primary types of stroke; ischemic stroke and intracerebral hemorrhage (Figure 1). Ischemic stroke constitutes approximately 85% and intracerebral hemorrhage constitutes about 10% of strokes in Western populations. The remaining 5% is composed of subarachnoid hemorrhages; however the latter type of stroke is largely considered separate from the former two types of stroke. When blood ceases to flow to an area of the brain, often caused by the occlusion of a cerebral or pre-cerebral artery, a cerebral infarction develops. The size of the necrotized area depends on the size of the affected vessel and on the amount of collateral blood flow to the area, which varies greatly from person to person. Ischemic stroke is often associated with generalized atherosclerosis that extends beyond the cerebral vascular system. When a blood vessel is obstructed, the adjacent brain tissue becomes ischemic, and neurological symptoms arise. Neurons, and later glial cells, rapidly perish without a blood supply. However, when the circulation is rapidly restored, and neurological symptoms remit within 24 hours, the incident is

defined as a transitory cerebral ischemia (TCI). Ischemic stroke is nearly always caused by either a thrombosis or emboli. A thrombosis is formed due to a lesion in the intimal layer of a vessel, typically in relation to an ulcerated atheromatous plaque. The thrombocytes aggregate and initiate the thrombotic process. Typically, the site of this process is the carotid bifurcation, but it may also occur in the vertebral and basilary arteries. Emboli most frequently originate in the heart, but they can also pass from artery to artery. Emboli most commonly affect the middle cerebral artery, due to its anatomical configuration. Another frequent mechanism of infarction is a degenerative transformation in the penetrating cerebral arteries, which cause an occlusion and an ensuing lacunar infarction.

Intracerebral hemorrhages are most often ascribed to structural weaknesses in the cerebral vessels, like aneurysms, which can rupture spontaneously or in connection with elevated blood flow and pressure in situations of physical strain. The hemorrhage then causes degeneration of neurons in the proximity of the ruptured vessel due to local mechanical damage and ischemia.

Several factors have been consistently associated with an increased risk of stroke. These risk factors reflect the fact that the pathogenesis of a stroke is similar to that of other common circulatory diseases; for example, ischemia of the heart and peripheral arterial disease. These established risk factors for stroke are typically classified as modifiable or nonmodifiable (Table 1).[8-10]

Table 1 Established risk factors for stroke

Nonmodifiable risk factors:
Age
Male gender
Ethnicity
Modifiable risk factors
Hypertension
Smoking

High alcohol intake
Diabetes mellitus*
Atrial Fibrillation*
Other cardiac diseases*
Carotid artery stenosis*
Low dietary intake of fruit and vegetables
Drugs

*Associated with ischemic stroke

The most well-established nonmodifiable risk factors for stroke include male sex and older age. Ethnicity also appears to be associated with the risk of stroke; i.e., a greater proportion of intracranial atherosclerotic strokes are found in Hispanics and African-Americans than in Caucasians. In contrast, a greater proportion of cardioembolic strokes are found in Caucasians than in Hispanics.[10]

Of the modifiable risk factors, hypertension and smoking are the most important, because they showed relatively strong associations with a high prevalence in most populations.[8-11] Hypertension alone was considered a predisposing factor in more than half of all patients with stroke.[12, 13]

However, despite the impact that the established risk factors have on stroke, other factors are also likely to be of importance. Stroke also occurs in subjects that were not exposed to the established risk factors;[8-10] this suggested that the established risk factors were not necessary components in the causation of all stroke events. Therefore, it is likely that other factors and either unknown or insufficiently studied mechanisms are associated with stoke.[8, 10, 14] Indeed, a large number of other factors have also been linked with an increased risk of stroke, including physical activity, obesity[8, 9], lipoprotein(a), von Willebrand factor (vWF), waist-to-hip ratio, white blood cell count, C-reactive protein, homocysteine, reactive oxygen species[10], hormone replacement therapy for post-menopausal women, antiphospholipid antibodies, and migraine.[8, 9] Although modest relative risk estimates have been reported for most of these potential risk factors, the high prevalence of these factors within most populations indicates that the risk of stroke attributable to these

potentially modifiable risk factors may be high. However, it is also likely that many of the possible risk factors are not causal, but are merely markers of increased risk.

1.3 Introduction to modern stroke care

In the early phase of a stroke, the affected brain tissue remains viable. Therefore, treatments in the early stages of stoke strive to reestablish blood circulation to the affected area. Stroke care varies according to the progression of the disease; different stages of care reflect the windows of opportunity for removing, reducing, or reversing the ensuing neurological and medical consequences of the stroke. A stroke is often accompanied by systemic vascular disease; thus, it is important to provide appropriate preventive treatment that targets other vascular areas beyond the cerebrovascular circulation.

1.4 Acute care

1.4.1 Specialized stroke units

The in-hospital stroke treatment setting and the composition of health care professionals treating the stroke patient are of great importance. A specialized stroke unit is defined as a hospital department/unit that is exclusively or primarily dedicated to patients with stroke and is characterized by multidisciplinary teams and a staff with a specific interest in stroke.[15, 16] A number of randomized clinical trials have shown that early admission to a specialized stroke unit can significantly reduce mortality, risk of disability, and risk of institutionalized care following a stroke.[16-18] Current Danish guidelines recommend that all hospitals that treat patients with stroke should establish a specialized stroke unit and that all patients admitted to a hospital with a stroke should be admitted to a specialized stroke unit.[15]

1.4.2 Computed tomography (CT) and magnetic resonance imaging (MRI)

An early, valid diagnosis is required for initiating an efficient care strategy for patients with acute stroke. A substantial proportion of patients exhibit stroke-like symptoms that are caused by other conditions, such as migraine, epilepsy, intracerebral tumors, infections, traumas, and metabolic illnesses.[19] Also, it is important to ascertain whether the stroke is caused by a hemorrhage or an occluded blood vessel, where the stroke is located, and how large an area it affects; all these factors will influence the ensuing care strategy. To a large extent, these factors can be identified with image diagnostics. CT or MRI scanning are equally effective in demonstrating acute cerebral

hemorrhage.[15] With conventional CT or MRI scanning, ischemic cerebral lesions will not be identified in 25% of stroke patients, however MRI with diffusion weighted imaging is superior to CT for identifying lesions in the brain stem and the cerebellum and for early identification of infarctions (within 12 h of symptom onset). [15] The current Danish guidelines recommend that all patients suspected of acute stroke should receive a CT or MRI scan with diffusion weighted imaging immediately after hospital admission or at least within the first day of hospitalization.[15]

1.4.3 Thrombolysis

Initially, the primary concern for an early stage stroke is to preserve viable brain tissue by reestablishing blood circulation. After CT/MRI has excluded a hemorrhage or tumor, the reestablishment of blood circulation can be attempted with acute thrombolytic treatment. This is typically performed with recombinant tissue plasminogen activator (rt-PA), which converts plasminogen in the blood into the active enzyme plasmin. Plasmin then breaks down fibrin, the cohesive material that holds the blood clot together. This treatment can be administered by injecting rt-PA either into a vein in the arm or, by a trained operator, into an artery. Although all the affected brain tissue may not be rescued by this procedure, it is possible to rescue the penumbra of the ischemic area, which receives some collateral blood flow from adjacent parts of the brain. The penumbra typically remains viable longer than the brain tissue near the occluded blood vessel. Acute thrombolytic treatment offers the potential of reduced neurological stroke symptoms, or even no neurological stroke symptoms, compared to no thrombolytic treatment. A number of randomized clinical trials that examined the efficacy of thrombolytic treatment and a Cochrane-review have demonstrated that thrombolytic treatment administered within 4½ h of stroke onset reduced the 3-month mortality, neurological deterioration, and dependency in daily living activities. The largest effect was observed among patients that were treated with the shortest time delay.[20-23] Two of these clinical trials demonstrated that treatment between 3 and 4½ h after stroke onset was beneficial compared to placebo, and did not significantly increase the risk of symptomatic intracranial hemorrhage.[22, 23] Current Danish guidelines recommend that intravenous thrombolysis with rt-PA is recommended in selected patients within 4½ h of stroke symptom onset, and emphasizes that the treatment should be initiated as early as possible.

1.4.4 Other care initiatives

Another stroke care strategy aims to prevent complications following a stroke, reduce stroke symptoms, and reduce the risk of new cardiovascular events, including another stroke. At hospital admission, a clinical assessment estimated that 9% of patients with stroke were undernourished. This condition is associated with an increased risk of complications, including infections, gastrointestinal hemorrhage, decubitus ulcers, and increased mortality.[24] Studies performed on Danish patients showed that an early nutritional evaluation can contribute to reduced mortality and shorter hospitalization.[17, 25] Current Danish guidelines recommend that an evaluation of the patient's nutritional risk should be performed as soon as possible after hospital admission, with subsequent weight control. Undernourished patients should be offered nutritional supplements that can improve protein and energy status.[15]

Following a stroke, patients that were rehabilitated and mobilized by physiotherapists and occupational therapists showed improved functional status and survival and reduced care requirements.[26-28] Current Danish guidelines recommend that, as soon as possible after hospitalization, the patient should be systematically assessed, and a plan should be made by an interdisciplinary team for positioning, mobilization, and rehabilitation. Moreover, mobilization and rehabilitation by specific physio- and occupational therapeutic initiatives should be commenced as soon as the patient's general condition is considered appropriate.[15]

Other treatment modalities and prophylactic initiatives include, but are not limited to, optimizing glycemic control for patients with diabetes, smoking cessation encouragement for smokers, nutritional risk evaluation, dietary counseling, antidepressive treatment, constipation treatment etc.[15]

1.5 Secondary Prophylaxis

1.5.1 Antithrombotic drugs

Among a variety of different antithrombotic drugs available for acute prophylactic treatment in patients with vascular disease, only acetylsalicylic acid (ASA) has been examined for patients with stroke.[29-31] Although antithrombotics are typically a secondary prophylactic treatment, they can also be part of the acute stroke treatment regimen; for example, ASA initiated within 48 h of a stroke onset can reduce the risk of death and reinfarction.[31] However, several large random

controlled trials (RCTs) showed inconsistent results for antithrombotic drugs in secondary prophylaxis; therefore, recommendations are equivocal for the choice of an antithrombotic. The choice of antithrombotic treatment for secondary prophylaxis depends on the type of stroke, the stage of the stroke, the presence of ischemic coronary disease or peripheral atherothrombosis, the adverse effects of the antithrombotic, the expected patient compliance etc.[15]

ASA irreversibly inhibits cyclooxygenase-1. This, in turn, inhibits the formation of thromboxane A_2 and the aggregation of platelets. The Antithrombotic Trialists' Collaborations meta-analysis has consistently shown that daily administration of ASA can reduce the risk of non lethal strokes, non lethal acute myocardial infarctions, vascular incidents, and mortality over an average of 29 months.[31] The current Danish guidelines recommend prophylactic ASA treatment with an initial dosage of 150-300 mg daily, followed by a maintenance dosage of 75 mg daily in patients with ischemic stroke.

Dipyridamol inhibits the uptake of adenosine in platelets. This increases c-AMP concentrations, inhibits platelet function, and, in addition, causes vasodilation. Large RCTs that tested patients with stroke or TCI demonstrated that a combination treatment of ASA plus dipyridamol was more efficient than ASA monotherapy for reducing the risk of stroke, acute myocardial infarction, or vascular death.[32-34] The current Danish guidelines recommend ASA (50-75 mg daily) in combination with dipyridamol (200 mg two times daily) as a prophylactic treatment for patients with ischemic stroke.[15]

Clopidogrel inhibits the binding of adenosine diphosphate (ADP) to ADP receptors. This inhibits platelet aggregation. Monotherapeutic clopidogrel has been shown to be more effective in reducing the risk of vascular events compared to monotherapeutic ASA, and it caused fewer bleeding complications compared to dipyridamol combined with ASA .[35, 36] The combination treatment of clopidogrel and ASA was not significantly different in efficacy compared to monotherapeutic ASA, but it incurred more hemorrhagic events.[37] Current Danish recommendations suggest clopidogrel as the first choice prophylactic treatment in patients with atherothrombotic stroke (i.e., patients with ischemic stroke and atherothrombosis in the coronary or peripheral vessels), in patients with ASA intolerance or allergy, in patients that experience adverse effects with ASA combined with dipyridamol, or in patients with recurring strokes.[15]

1.5.2 Anticoagulants

Embolisms in the brain often originate from the heart, and the heart is especially prone to forming clots during atrial fibrillation (AFLI). AFLI causes the left atrium of the heart to vibrate irregularly, thereby altering the hemodynamics and rendering the blood more liable to coagulate and form clots. The risk of a reinfarction in patients with AFLI and stroke can be reduced, with anticoagulant treatment, from approximately 12% to 4% per year; moreover, the incidence of severe bleeding complications is fairly low (2.8% per year), relative to patients not treated with anticoagulants (0.7% per year).[38-40] Therefore, eligible patients with ischemic stroke and AFLI should receive prophylactic treatment with anticoagulants. Nevertheless, several studies have shown a lack of anticoagulant therapy implementation in secondary prophylaxis.[41-45] Anticoagulant therapy requires strict vigilance and attention towards the thrombo-hemorrhagic balance. When correctly administered, anticoagulant therapy provides a high effect sufficient to effectively prevent ischemic stroke, but also remains sufficiently low to avoid significantly increasing the risk of hemorrhage, including hemorrhagic stroke.

Presently, anticoagulant drugs used for treatment are vitamin K antagonists. Vitamin K antagonists indirectly inhibit the formation of coagulations factors II, VII, IX, and X and coagulation inhibitors, proteins C and S. The optimal time is not clearly defined for initiating oral anticoagulant therapy following a stroke. Early initiation of the treatment may incur the risk of a hemorrhagic transformation of the stroke. Current Danish guidelines recommend that anticoagulant therapy with vitamin K antagonists should be initiated within two weeks of stroke onset in patients with ischemic stroke and AFLI, when there are no contraindications. In case of contraindications, ASA can be used as an alternative. Anticoagulant therapy is not indicated in patients with non-cardioembolic stroke.[15]

1.5.3 Antihypertensives

An essential part of prophylactic treatment is to lower the blood pressure in patients who have experienced a stroke in order to reduce the risk of recurrent stroke or other cardiovascular events. The therapeutic goal following a stroke is to attain a blood pressure of 130/80 mmHg, according to recommendations from the European Society of Hypertension. However, of note, no studies have identified a lower limit for optimal blood pressure. Therefore, essentially, the goal is to reduce blood pressure to the lowest tolerable level; i.e., as low as possible without inducing symptoms or

problems associated with hypotension. There are several therapeutic strategies for reducing blood pressure. First, blood volume can be reduced with diuretics; alternatively, arterial pressure can be reduced with vessel dilating drugs. Often, combinations of antihypertensive drugs are required to reach the therapeutic goal. There is no general consensus on the first choice for antihypertensives; however, in general, it appears that the type of antihypertensive drug is probably less important than attaining sufficient intensity.[46-48]

A number of large RCTs have investigated the effects of antihypertensive treatments on patients with stroke.[49-51] These trials have shown an overall positive effect of reducing blood pressure for reducing the risk of recurrent stroke. The effect of angiotensin converting enzyme inhibitor (ACE-inhibitor) monotherapy has not been documented, but thiazide diuretic monotherapy was associated with a reduced risk of stroke over a period of three years.[49] Moreover, the combination of an ACE-inhibitor and a thiazide diuretic displayed an improved effect compared to thiazide diuretic monotherapy.[51] Dementia and cognitive difficulties can be reduced by avoiding a recurrent stroke, as can the extent of handicaps, and dependency in daily activities.[52, 53] However, reducing the blood pressure did not appear to have an independent neuroprotective effect.[54]

Thiazide diuretics are most commonly used in prophylactic stroke treatment, but other diuretics primarily aimed at prophylactic treatment for heart diseases are also effective for preventing recurrent stroke. The vessel dilating drugs most commonly used in stroke prophylaxis are ACE-inhibitors, angiotensin II antagonists (ATII antagonists), and calcium channel blockers.

The collective results of several studies showed that effective prevention of recurrent strokes and vascular incidents can be attained with good control of blood pressure. Current Danish recommendations state that, for hypertension after an ischemic or hemorrhagic stroke, antihypertensive treatment should be initiated when the condition is stable; furthermore, in patients under age 75, antihypertensive treatment should be considered regardless of blood pressure. A combination treatment of ACE-inhibitor with a diuretic is more efficient for preventing recurrent stroke than monotherapeutic ACE-inhibitor treatment. Also, ATII antagonists can effectively prevent recurrent stroke and other vascular incidents among patients with stroke. ATII treatment can be initiated when a hemodynamic stroke is excluded and the condition is stable, regardless of blood pressure. Finally, the recommendations state that, in patients with acute

intracerebral hemorrhages, aggressive antihypertensive treatment can be initiated within 6 h of stroke onset to prevent recurrent hemorrhage.[15]

1.5.4 Statins

Statins, often referred to as "lipid lowering drugs", are widely used drugs that effectively reduce the risk of cardiovascular events through a reduction in blood cholesterol. Statins inhibit the enzyme, hydroxymethylglutaryl-CoA reductase (HMG-CoA reductase), which represents the rate limiting step in the mevalonate pathway for cholesterol synthesis in the liver. The statin-induced reduction in blood cholesterol slows the progression of atherosclerosis, and, in some cases, may even reverse the process. This, in turn, reduces the risk of reinfarction or other cardiovascular events. Large RCTs have shown that statin treatment for patients with stroke or cardiovascular disease reduced the risk of death or reinfarction compared to placebo.[55, 56] Current Danish guidelines recommend that patients with dyslipidemia should be instructed in a cholesterol-lowering diet and treated with statins, with a therapeutic goal of lowering total serum cholesterol concentrations to less than 4.5 mmol/l and low density lipoprotein (LDL) cholesterol concentrations to less than 2.5 mmol/l. Also, in some cases, although total serum cholesterol and LDL-cholesterol are below these limits, lipid lowering treatment may be indicated in patients with atherothrombotic stroke and a high risk of new cerebrovascular or coronary ischemic events.[15]

1.5.5 Carotid CT-angiography/ultrasound

A common source of emboli is atherosclerotic sedimentation in the carotid bifurcation. A severe stenosis in the carotid artery in combination with a poor collateral blood supply can give rise to cerebral hypoperfusion. However, that condition is relatively uncommon, and further examination is relevant, primarily in patients with signs of an ischemic attack localized to regions supplied by the carotid arteries. The severity of a carotid stenosis can be evaluated with CT-angiography or ultrasound examination. In severe cases of symptomatic stenosis in the carotid artery, prophylactic removal of the stenosis, or an endarterectomy, can reduce the risk of stroke in some patients.[57, 58] Current Danish guidelines recommend that early imaging diagnostics, ideally within 24 h, must be performed in order to identify symptomatic carotid stenoses eligible for carotid endarterectomy. Operative removal of a symptomatic carotid stenosis that occludes more than 70% of the lumen is recommended unless the patient is experiencing severe sequels from a previous stroke or has an incurable disease. This procedure should be performed as soon as

possible and preferably within a few days of the primary event. Also, patients with moderate stenosis should be offered an operation when it can be performed within the 24-h timeframe.[15]

1.6 Age, sex, and variation in quality of care

Stroke is a serious clinical event that occurs independent of age and sex.[59] Although stroke in all afflicted patients is associated with increased mortality and reduced functional status, this is especially true for older patients.[8, 60, 61] Danish and international guidelines for stroke care recommend the same level of care for everyone, independent of age and sex. Yet, indications have been reported of age- and sex-related differences in the level of stroke care for different populations and this has become a hot topic of debate, particularly in the new millennium. A number of studies have identified age-related differences in the quality of stroke care; however, there appears to be uncertainty about whether sex-related differences also exist in stroke care. This section presents an overview of the international research on age- and sex-related differences in stroke care (Table 2). The overview will primarily focus on research that investigated age- and sex-related differences in relation to the areas of acute care and secondary prophylaxis outlined in the above introduction to modern stroke care.

The PubMed literature was reviewed using the MeSH terms "*stroke"* or *"cerebral infarction"* alone, and in combinations with the following MeSH terms; *"age factors", "aged", "aged, 80 and over", "quality of health care", "quality indicators", health care*", *"health resources", "male", "female", "sex characteristics" , "sex distribution", "anticoagulants", "platelet aggregation inhibitors", "anti hypertensive agents", "hydroxymethylglutaryl-CoA-reductase inhibitors", " atrial fibrillation", and "treatment outcome"* . The search was limited to include only English- and Danish-language studies in humans. Additional studies were identified from the reference lists of the publications selected in the search.

1.7 Acute care

1.7.1 Age-related differences

A number of studies have examined the association between age and different types of acute care in stroke patients, including, e.g., diagnostic imaging, admission to a specialized stroke unit, and antithrombotic therapy. In a prospective joint European study (Di Carlo et al., 1999) involving 7 countries and 4499 patients[62], they found that brain imaging and other diagnostic tools were less frequently used in older patients; only 66.9% of patients ≥80 years old received brain imaging compared with 87.7% of patients <80 years old. Another European study (Bhalla et al., 2004) on 1847 patients with stroke from 13 hospitals in 10 countries found that patients ≥75 years old received less intensive diagnostics, care, and rehabilitation compared to patients <75 years old.[63] Thus, a lower proportion of the patients that were ≥75 years old vs. those <75 years old were examined with CT scanning (87% vs. 79%), angiography (1% vs. 11%), echocardiography (34 vs. 17%), or Doppler analysis (22% vs. 41%). For older patients, the lack of brain imaging (OR=0.2, 95% confidence intervals (CI): 0.01-0.6) was significantly related to mortality at 3 months. The study also found differences in other care initiatives; fewer patients ≥75 years old compared to those <75 years old were transferred to a rehabilitation ward upon discharge (13% vs. 17%). At 3 months after the stroke, a lack of physio- and ergotherapeutical effort was detected; fewer older patients compared to younger patients received physiotherapy (19% vs. 24%) and occupational therapy (4% vs. 9%).[63] However, on average, only one hospital per country was included in that study; therefore, the results might not be representative of the general practice in an individual country. Also, a variety of different models for stroke care and treatment might exist in the included countries. Thus, the final results might not accurately reflect the standards of an individual country. On the other hand a recent American study published in 2010 by Fonarow et al, performed on 502 036 ischemic stroke patients registered in the Get With the Guidelines (GWTG)-Stroke program from 2003 to 2009, found that age-related differences in acute treatment with thrombolysis and early antithrombotic treatment improved substantially over time in all age-groups.[64] However, participation in the GWTG-Stroke program is voluntary for hospitals in the US, and those that participate are more likely to be larger teaching hospitals with a special interest in stroke care and quality improvement.[64]

1.7.2 Sex-related differences

To date, reports have been inconsistent on sex-related differences in acute stroke care. In a Canadian study, Kapral et al (2005) found that there were no sex-related differences in the use of neuroimaging, thrombolysis, and antithrombotic treatment, and that, after adjustment for age, women were as likely as men to receive care in an acute stroke unit.[65] The study also investigated the use of other acute care initiatives, including assessments in occupational therapy, physiotherapy, speech pathology, and carotid imaging. Again, they did not find any sex-related differences. However, that study would be primarily generalizable to subgroups of patients with moderate severity stroke, because patients were required to have surrogate consent to participate; thus, some patients with severe or fatal stroke were excluded because they were unable to give consent, and some patients with minor stroke or TIA were discharged before they could be asked to participate. An American study on 6690 patients by Smith et al (2009) also found no sex-related differences in acute stroke care. The authors used a state-wide database, based on the American Stroke Association's patient management tool, 'Get with the Guideline-Stroke' (GGS), to explore sex-related differences in stroke presentation and care. [44] Among other things, that study investigated the use of rt-PA in patients with ischemic stroke, and they found no sex-related differences. They also detected no sex-related differences in the proportion of patients admitted to a neurology ward or a specialized stroke unit. A German prospective cohort study on 558 patients by Müller-Nordhorn et al (2006) found only few sex-related differences in medical management after stroke or TIA; however, they did find that women were more likely to receive hypoglycemic agents in the acute management phase.[66] A recent Swedish study by Eriksson et al (2009) performed on 24 633 patients admitted with stroke also found no sex-related differences in acute care.[67] In that study, the authors found no differences in the use of CT-scanning or thrombolytic therapy (OR=1.007, 95%CI: 0.828-0-1.225 and OR=0.989, 95%CI: 0.807-1.212, respectively with males as a reference). They did, however, initially find a sex-related difference in stroke unit care that was not explained by an older mean age in women; nonetheless, this difference became small and nonsignificant after adjusting for the level of consciousness at admission.[67] A Swedish meta-analysis by Appelros et al (2009), which included the results from 90 papers, supported the notion that sex-related differences in stroke treatment and outcome were small, with no unequivocal proof of sex discrimination.[68] In that analysis, the authors found that most studies reported no sex-related differences in the access to stroke units and in rehabilitation;

moreover, the differences found, e.g., in the access to thrombolysis, could be explained by the fact that women were typically older at stroke onset and had more severe strokes than men.[68]

In contrast, other studies have found sex-related differences in acute stroke care.[43, 69-72] One of these, a large German study by Foerch et al (2007), found sex-related differences in early hospital admission and in the use of thrombolytic treatment. Thus, after multivariate adjustment, women were overall 10% less likely than men to be admitted within the first 3 h of stroke onset, and that percentage decreased further for older women. Furthermore, women ≥74 years old were 25% less likely to receive treatment compared to men of the same age.[69] Part of these sex-related differences in admission time and use of thrombolytic treatment could probably be explained by the sociodemographic fact that "surviving spouses" are more likely to be women than men and that older women are, therefore, more liable to live alone than elderly men; however it is unlikely that this would account for all the observed differences. In an America study, Gargano et al (2008) also found that, although considerable parity exists in many aspects of stroke care, women were less likely to receive thrombolytic treatment even after adjustment (rt-PA; OR=0.56; 95% CI:0.37-0.86).[72] Reeves et al (2009) also found sex-related differences in the use of thrombolytic treatment in a large American study.[73] In that study, among 14 460 patients with ischemic stroke who arrived at hospital within 2 h of symptom onset, only 55.8% of women received intravenous rt-PA compared to 59.4% of men (P<0.0001). Later, Reeves et al (2009) published a meta-analysis, where they also found that women with acute stroke were consistently less likely to receive thrombolysis treatment compared to men.[43] The analysis was performed on 18 studies, and the combined odds ratio (OR) was 0.70 (95%CI: 0.55–0.88); this indicated that women had a 30% lower odds of receiving rt-PA treatment compared to men. However, a wide range of study designs were included; thus, it was not possible to apply the original study quality criteria outlined in the review protocol. Furthermore, the substantial between-study variability, and the inconsistent recording of demographics for the male and female study populations in the different studies made it difficult to abstract the information.

Reeves et al also found that women were less likely to receive early antithrombotic treatment compared to men.[73] Early antithrombotic treatment was defined as antithrombotic medication administered within 48 h of admission, the same definition used in the Danish stroke guidelines.

They found that, in 245 500 patients with ischemic stroke, 93.6% of women received early antithrombotics compared to 94.7% of men. Although the absolute difference appeared to be small, it was based on many observations and was statistically significant (P<0.0001).

Other studies have reported sex-related differences in the time delay from when the patient arrives at the hospital to the time the patient is examined by a physician.[70] Gargano et al found that women with acute stroke experienced greater emergency department delays than men; this could not be ascribed to differences in presenting symptoms, time of arrival, age, or other potential confounding factors.[70] Compared to men, women waited 11% longer before examination by a doctor (adjusted time ratio (TR) 1.11, 95% CI: 1.02–1.21). However, this difference was only observed among patients who arrived more than 6 h after symptom onset; for patients who arrived within 6 h of symptom onset, the door-to-doctor time ratio for women compared to men was smaller and nonsignificant (TR=1.05, 95%CI: 0.92–1.21). Furthermore, that study found statistically significant sex disparities in door-to-image time. This was defined as the time from arrival at the hospital until diagnostic imaging of the patient with stroke. Here, the adjusted difference in the time ratio between women and men was 1.15 (95%CI; 1.08–1.23); unlike the sex differences in door-to-doctor time, these differences remained evident after restricting the analysis to patients who arrived within 6 h, or even 2 h of symptom onset.[70] Likewise, a large European study performed by Di Carlo et al (2003) found that sex-specific differences existed in some aspects of acute care. That study showed that women received less diagnostic investigation with medical resources compared to men, including brain imaging (77.1% vs. 85.7%), Doppler examination (32.8% vs. 44.0%), echocardiogram (22.8% vs. 30.5%), and angiography (9.5% vs. 5.5%).[71] However, the authors detected no sex-related differences in physiotherapy, speech therapy, or occupational therapy, in accordance with the findings of Kapral et al. Although the proportion of patients who received rehabilitative services during hospitalization varied between different studies, the pattern of no detectable sex differences can be found back to 2000. For example, Holroyd-Leduc et al (2000) performed a Canadian study on approximately 45 000 patients, and no sex-related differences were detected in the use of occupational therapy, physiotherapy, or speech/language pathology assessment.[74]

1.8 Secondary prophylaxis

1.8.1 Age-related differences

Some studies have indicated that medical secondary prophylaxis following a stroke is not sufficiently implemented among older individuals. Lamassa et al (2001) performed a European concerted action study involving seven countries, where they investigated the characteristics, outcome, and care of stroke associated with atrial fibrillation. They found that, for stroke patients with atrial fibrillation, increasing age was the only independent determinant for lack of treatment with anticoagulants.[42] A Swedish study by Glader et al (2010) found in 21 077 patients with stroke that there was a similar age-related difference in the use of medical prophylaxis.[75] In that study, the authors found that advanced age was strongly associated with reduced persistence of anticoagulant therapy at two years after a stroke. The possible implications of these differences are underlined by recent findings from the Atrial Fibrillation Investigators.[76] In a meta-analysis based on patient-level data from 8932 patients with AFLI from 12 trials, van Walraven et al found that the relative efficacy of antiplatelet treatment for preventing ischemic stroke appeared to decrease with increasing age, but the efficacy of oral anticoagulant therapy was independent of age. The risk of stroke increases with age; thus, older patients receive a higher absolute benefit from oral anticoagulant therapy than younger patients. Nevertheless, there is always the concern that anticoagulant therapy carries the risk of hemorrhage as an adverse effect; however, a study by Fang et al (2006) that included 13 559 patients with nonvalvular AFLI indicated that carefully monitored warfarin therapy could be used with reasonable safety in older patients.[77] In that study, Fang et al found that the risk of major hemorrhage, particularly intracerebral hemorrhage, in patients with AFLI increased with age, regardless of whether the patients were taking warfarin. This indicated that the prophylactic benefit of carefully monitored anticoagulant therapy outweighed the risk of hemorrhage. However, the study was not performed exclusively on patients with AFLI who had previously experienced a stroke; therefore, the risk of major hemorrhages might be different in a population that included only patients with stroke.

On the other hand not all studies support the existence of age-related differences in secondary medical prophylaxis. The study from 2010 by Fonarow et al, in which the authors found that acute treatment has improved substantially over time in all age-groups, also found no substantial age-related differences in use of antithrombotics and anticoagulants at hospital discharge.[64] However,

this study only included in-hospital performance measures and had no data on post discharge care and outcomes.

Other types of medication have also been found to be underused for secondary medical prophylaxis following a stroke. Ovbiagele et al (2006) found that statin use during hospitalization appeared to be used insufficiently;[78] moreover, a study by Lalouschek et al (2003) found that statins were used less in eligible older patients than in eligible younger patients.[79] In that Austrian study, Lalouschek et al found that, among 1743 patients admitted with ischemic stroke between 1998 and 2001, those aged 75–80 years and ≥85 years had lower odds ratios (OR=0.5; 95%CI:0.3–0.9, and OR=0.2; 95%CI: 0.1–0.3, respectively) of receiving statin treatment compared to patients <55 years.[79]

However, some types of medical prophylaxis appeared to be used more frequently among older patients compared to younger patients. In a retrospective cross-sectional study on 10 076 patients with stroke by Simpson et al (2005), the authors found that patients >75 years old with ischemic stroke received antiplatelet therapy more often than patients <75 years old (OR=1.83; 95%CI:1.64-2.06); similar findings were reported by Glader et al (2010) in patients studied two years after a stroke.[75, 80]

Age-related differences in secondary prophylactic stroke care may also occur in care modalities other than drug treatment. In a British study, Fairhead and Rothwell (2006) found that, although the incidence of carotid stenosis increased steeply with age, there was substantial underuse of carotid imaging in routine clinical practice for patients ≥80 years with transient ischemic attack or ischemic stroke.[81] They compared routine clinical practices in the Oxfordshire Primary care Trust with prospectively collected data in the first year of the Oxford vascular study (OXVASC). The participants of the OXVASC study were included in the Oxfordshire Primary Care Trust population. Fairhead and Rothwell reported that the rates of carotid imaging increased with age in both populations, but the rate decreased in patients aged ≥80 years in routine clinical practice (relative rate=0.36, 95%CI: 0.28-0.46). Also, the same pattern was observed in patients with diagnoses of 50–99% symptomatic stenosis; despite the fact that the OXVASC study showed a steep increase in the rates of symptomatic carotid stenosis in patients aged ≥80 years, the rate of imaging dropped in routine clinical practice for those patients. Furthermore, compared to the OXVASC population,

the rates of carotid endarterectomy for recently symptomatic carotid stenosis was also substantially lower for patients aged ≥80 years in routine clinical practice (relative rate=0.19, 95%CI: 0.06–0.63). This suggested that, based on the steep rise observed in the rates of carotid endarterectomy in patients aged ≥80 years in the OXVASC study, the fall observed in rates of older patients undergoing surgery in clinical practice was unlikely to have been explained by contraindications to treatment or to patient choice.

1.8.2 Sex-related differences

Eight different studies looked at medical prophylactic treatment. Of those, five studies appeared to agree on the existence of sex-related differences [44, 73, 74, 80, 82], but three studies and a meta analysis found no significant sex-related differences.[66-68, 72] In a study by Gargano et al (2007), the authors found no sex-related differences in the use of antithrombotic treatment, even after adjustment for age and prognostic factors (OR=0.93, 95%CI:0.70-1.24).[72] In another study by Müller-Nordhorn et al (2006), no sex-related differences were found in diagnostic procedures or in follow-up management after stroke or TIA.[66] The Swedish study by Eriksson et al (2009) also found no differences in the use of antithrombotic, antihypertensive, or oral anticoagulant therapies at discharge (OR=1.060, 95%CI: 0.982-1.144; OR=1.028, 95%CI: 0.964-1.096, and OR=0.994, 95%CI: 0.835-1.183, respectively, with males as a reference).[67] However, that study also found that women were less likely than men to receive lipid-lowering therapy (OR= 0.811, 95%CI: 0.765-0.860). In the meta-analysis by Appelros et al (2009), no unequivocal proof was found of sex-related differences in use of aspirin or warfarin.[68]

Other studies have pointed towards the existence of sex-related differences. In the American study by Reeves et al (2009), the sex-related differences found in acute treatment appeared to carry over into medical prophylaxis. At hospital discharge, women were less likely than men to receive antithrombotic therapy and anticoagulant therapy.[73] However, the absolute differences were not large (94.3% and 95.2% for antithrombotics and 88.0% and 89.7% for anticoagulants, for women and men, respectively). That study also investigated differences in lipid lowering agent prescriptions at hospital discharge; there, the sex-related differences were more pronounced (69.3% in women versus 76.1% in men). Similarly, a Swedish study by Glader et al (2003) that included 19 547 patients admitted with stroke found sex-related differences in medical prophylaxis.[83] In that study, at discharge from the hospital, women received antithrombotic agents

for secondary stroke prevention less often than men (OR=0.86 95%CI: 0.76-0.98), and women with AFLI were treated with anticoagulants as secondary prevention less often than men (OR=0.75 95%CI: 0.68-0.93).[83] Another study by Fang et al (2005) that included 13 559 patients with AFLI suggested that reduced prophylaxis might hold substantial clinical consequences.[82] In their study, Fang et al found that, in the absence of warfarin treatment, women were at higher risk than men for AFLI-related thromboembolism, with a relative risk (RR) of 1.6 (95%CI: 1.3-1.9). Additionally, they found that warfarin therapy appeared to be equally or more effective for reducing the rate of thromboembolism (most of which were stroke) in women compared to men (RR=0.4, 95%CI: 0.3-0.5 and RR=0.6, 95%CI: 0.5-0.8, respectively), with similar rates of major hemorrhage.[82] However, that study did not restrict inclusion to patients with a previous history of stroke; therefore, the sex-related differences might be different in a restricted population. Holroyd-Leduc et al also found sex-related differences in the use of medical prophylaxis after hospital discharge.[74] They found that women ≥85 years old were less likely than men of the same age to receive aspirin and ticlopidine (30.7% vs. 36.0% and 6.8% vs. 9.2%, respectively); on the other hand, they also found that men and women were equally likely to receive warfarin after a stroke.

This overall picture of sex-related differences in medical prophylaxis was supported by a U.S. study by Smith et al (2009).[44] Overall, they concluded that high lipid levels were treated less aggressively and antithrombotics were used less commonly in women than men. Interestingly, at the time of discharge, only 84.9% of women were treated with anticoagulants compared to 88.6% of men (P<0.0001); nevertheless they found no sex-related differences in antithrombotic treatment by day two of hospitalization (83.4% in women and 82.2% in men; P=0.21). Also, they found that, at discharge, more women than men received no cholesterol lowering drugs (30.0% of women and 25.0% of men, P<0.001). That finding was supported by two earlier studies; one by Gargano et al (2007), who found that lipids were less often tested in women compared to men (OR=0.76; 95%CI: 0.61–0.94) and the other by Eriksson et al.[67, 72]

Also, Simpson et al (2005) found sex-related differences in medical prophylaxis.[80] They observed that women with any kind of stroke were more likely to receive a thiazide diuretic (OR=1.60, 95%CI: 1.46-1.75), but less likely to receive an ACE inhibitor (OR=0.73, 95%CI: 0.67-0.81) than men. Additionally, they found that women with ischemic stroke were less likely than men to receive

either an antithrombotic (antiplatelets or warfarin; OR=0.84; 95%CI: 0.75-0.94) or statin therapy (OR=0.82, 95%CI: 0.74-0.90). Women with AFLI received warfarin less often (OR=0.62, 95%CI:048-0.81), but antiplatelet therapy more often (OR=1.30, 95%CI:1.00-1.68) than men.[80]

1.9 Summary

In the above reviewed studies, both adjusted and unadjusted overall mortality appeared to increase with increasing age. However, while unadjusted mortality and mortality rates initially appeared to be higher in women compared to men, the adjusted mortality indicated that women had a stroke survival advantage compared to men.[84] This leap in adjusted vs. unadjusted inter-sex mortality appeared to be partly caused by the fact that a larger proportion of older patients with stroke were women; but, even taking this into account, the female sex appeared to be associated with better long term survival.

In summary, existing investigations found a variety of age- and sex-related differences in acute care and prophylactic initiatives for patients with stroke. Overall, in patients with stroke, age differences appear to exist in acute care, use of carotid imaging and secondary prophylactic treatment. In contrast, the data on sex-related differences were more inconsistent and were sometimes difficult to interpret. In general, the sex-related differences that were reported were small for most of the investigated parameters. Also, different care modalities were difficult to directly compare, because the different studies sometimes used different ways of measuring and evaluating the data. Few studies that focused on sex-related differences in care and outcome investigated whether the observed differences might, in fact, have been attributable to age-related differences, particularly given the relatively high mean age of female patients with stroke. Many studies were based on selected patient populations, lacked detailed data on diagnosis and care (in particular, the timing of specific interventions), and had incomplete follow-up. Likewise, many studies did not examine whether, or to what extent, the possible differences in care could explain the age- and sex-related differences in mortality among patients with stroke.

Table 2 Overview of discussed stroke related studies

Subject *(subject overlaps)*	**Author, year, country**	**N**	**Study design**	**Inclusion criteria**	**Outcome**	**Conclusions**
Age differences in acute care.	Di Carlo *et al.* 1999, Italy[62]	4499	Follow-up study	Stroke	3 month disability	Brain imaging and other diagnostic tool were less frequently used in patients aged 80 years or more.
	Bhalla *et al.* 2004, UK[63]	1847	Follow-up study	Stroke	3 month mortality	A less intensive effort for diagnostics, care and rehabilitation of patients aged ≥75 years compared with patients aged <75 years was found.
	Fairhead and Rothwell. 2006, UK[81]	680 772	Comparative populations based follow-up studies.	Stroke, TIA	Age specific rates of carotid imaging	Patients aged 80 or above are under investigated with carotid imaging in routine clinical practice despite the fact that the incidence of symptomatic carotid stenosis increases steeply with age.
Acute and secondary	Fonarow *et al*. 2010, USA[64]	502 036	Follow-up study	Ischemic stroke	In-hospital performance measures and mortality	Performance measure-based treatment rates improved substantially over time for ischemic stroke patients in all age groups, resulting in

						smaller age-related treatment gaps.
Sex differences in acute care.	Foerch,C. *et al*. 2007, Germany.[69]	53 414	Follow-up study	Stroke	Acute stroke management	Women receive poorer acute stroke management than men, which is best explained by the fact that "surviving spouses" are more likely to be women than men.
Acute and secondary	Di Carlo *et al*. 2003, Italy.[71]	4499	Follow-up study	Stroke	3 month death, disability and handicap	Women receive lower quality of in hospital diagnostics. Both medical and sociodemographic factors may significantly influence stroke outcome. No sex differences in physiotherapy, speech therapy or occupational therapy was observed.
Acute and secondary	Gargano,J.W. *et al*. 2008, USA.[72]	2566	Retrospective follow-up study	Acute stroke	Thrombolytic treatment, in-hospital treatments, and in-hospital procedures	Women were less likely than men to receive thrombolytic treatment and lipid testing, even after adjustment. No sex differences were observed in the use of antithrombotic or anticoagulant treatment.
Acute and secondary	Reeves,J.M. *et al*. 2009, USA.[73]	383 318	Follow-up study	Ischemic stroke	Length of stay, mortality, ambulatory status	Quality of care for women (including IV thrombolysis,

					and discharge destination	antithrombotics, anticoagulant therapy and lipid lowering treatmetn) was lower than that for men, and women were less likely to be discharged home.
Acute and secondary	Appelros *et al*. 2009, Sweden[68]	Meta analysis of 90 studies	Meta analysis	Stroke	Thrombolysis, stroke unit care, secondary prevention, surgical treatment and prevention.	Sex differences in stroke treatment are small with no unequivocal proof of sex discrimination. Women have poorer functional outcome because of higher age at stroke onset and more severe strokes.
	Reeves,J.M. *et al*. 2009, USA.[43]	Meta analysis of 18 studies	Meta analysis	Acute ischemic stroke	Thrombolysis treatment	Women with acute stroke were consistently less likely to receive thrombolysis treatment compared with men
	Eriksson *et al*. 2009, Sweden[67]	24 633	Follow-up study	Acute stroke	In-hospital care, 3 month mortality and 3 month residential status	There were no sex-related differences in use of stroke unit care, probability of receiving thrombolysis, oral anticoagulant therapy or antiplatelets.
Acute and secondary	Kapral,M.K. *et al*. 2005, Canada.[65]	3323	Follow-up study	Acute stroke	In-hospital stroke management, long term care and 6 month mortality .	No major sex differences in stroke presentation or management were found except for lipid

						measurement where women were less measured than men.
Acute and secondary	Müller-Nordhorn *et al*. 2006, Germany.[66]	558	Follow-up study	Stroke, TIA	Acute and long term management of stroke	Only few sex differences in medical management after stroke or TIA, with the exception that women were more likely to receive hypoglycaemic agents in the acute management phase.
Age differences in secondary prophylaxis	Lamassa,M. *et al*. 2001, Italy.[42]	4462	Follow-up study	Acute stroke	3 month survival, disability and handicap in stroke patients with AFLI compared to stroke patients without AFLI.	For stroke patients with AF, increasing age was the only independent determinant of not being on anticoagulants.
	Van Walraven,C. *et al*. 2009, Cananda.[76]	8932	Analysis of patient level-data from 12 randomized trials of stroke prevention in atrial fibrillation.	AFLI	Ischemic stroke, serious bleeding and cardiovascular events	The relative efficacy of antiplatelet treatment to prevent ischemic stroke appears to decrease with increasing age, whereas it does not change for oral anticoagulant therapy.
	Ovbiagele,B. *et al*. 2009, USA.[78]	2894	double-blind, randomized controlled clinical trial	Ischemic stroke	Statin treatment	Only half of those eligible for treatment were given statins, and of those receiving statin treatment, less than half were within recommended lipid goals

	Lalouschek,W. *et al*. 2002, Austria.[79]	1743	Follow-up in a Prospective cohort study	Ischemic stroke or TIA	Statin treatment	Eligible patients aged 75 years or more were less likely to receive statin treatment compared to patients below 55 years
Age and sex differences	Simpson *et al*. 2005, UK.[80]	10 076	Follow-up	Stroke, TIA	Secondary medical prophylaxis	Ischemic stroke patients older than 75 years received more antiplatelet therapy than patients younger than 65 years. Women with any stroke were more likely than men to be prescribed thiazide, but less likely to be prescribed an ACE inhibitor. Women with ischemic stroke were less likely to receive antiplatelet, warfarin or statin treatment than men.
	Glader *et al*. 2010, Sweden.[75]	21 077	Follow-up	Stroke	Secondary medical prophylaxis	Persistent secondary treatment declines rapidly during the first two years after stroke, especially for statins and warfarin.
Sex differences in secondary prophylaxis	Holroyd-Leduc,J.M. *et al*. 2000, Canada.[74]	44 832	Follow-up study	Acute stroke	Sex differences in comorbidities, the use of rehabilitative	No sex differences in use of occupational therapy, physiotherapy or speech/language

					services, the use of antiplatelet therapy and anticoagulants, discharge destination, and mortality.	pathology assessment. However, elderly men are more likely than elderly women to receive aspirin and ticlopidine and equally like to receive warfarin after a stroke. Despite these differences, elderly women have a better 1-year survival after a stroke.
	Glader *et al*. 2003, Sweden.[83]	19 547	Follow-up study	Acute stroke	Sex differences in comorbidities, stroke unit care, the use of antiplatelet therapy and anticoagulants and institutional living at 3 months	Sex-related differences exist in use of secondary medical prophylaxis
	Smith,D.B. *et al*. 2009, USA.[44]	6690	Follow-up	Stroke, TIA, subarachnoid hemorrhage.	Various clinical interventions and treatment.	Lipids were less aggressively treated and antithrombotics were less commonly used in women.

1.10 Effectiveness of secondary medical prophylaxis in patients with stroke

1.11 Definition of efficacy and effectiveness

In a health care context, *efficacy* describes the capacity for a given intervention (e.g., a drug) to provide a beneficial change or therapeutic effect under optimal conditions. To establish efficacy, a given intervention should be at least as beneficial as other available interventions, to which it will have been compared. These types of comparisons are typically made in randomized controlled trials, in which patients are often highly selected and the intervention is closely monitored. In contrast, in real-life situations, patients are not highly selected, and they may fail to follow medical advice, which could result in different success rates from those reported in clinical trials. Therefore, *effectiveness* describes the capacity for a given intervention to provide a beneficial change or therapeutic effect in real-life settings.[85]

In summary, *efficacy* and *effectiveness* are measured under two different conditions; the first describes how well an intervention works under ideal conditions, and the second describes how well an intervention works in ordinary circumstances.

1.12 Existing research

In primary stroke prophylaxis, drug effectiveness is measured as the ability of different drugs, alone or in combination, to reduce the risk of stroke; in secondary stroke prophylaxis, drug effectiveness is measured as the ability of different drugs, alone or in combination, to reduce the risk of adverse outcomes, including death and cardiovascular events, in patients who have experienced a stroke. Few studies have examined the effect of the various types of primary medical stroke prophylaxes outside large clinical trials; even fewer studies have investigated the effect of the various secondary medical stroke prophylaxes in real-life settings. This section presents an overview of the international research on the effectiveness of drugs used in stroke prophylaxis. The overview will focus on presenting research on effectiveness of secondary prophylaxis when available; for drugs where research on effectiveness in secondary prophylaxis is unavailable the overview will focus on effectiveness in primary stroke prophylaxis.

A literature search was performed in PubMed with the following MeSH terms "*stroke"* or *"cerebral infarction"*, with combinations of the following MeSH terms; *"anticoagulants", "anticoagulant", "platelet aggregation inhibitors", "antiplatelets"[All Fields], "anti hypertensive agents", "adrenergic beta-antagonists", "adrenergic"[All Fields] AND "beta-antagonists"[All Fields], "statin", "hydroxymethylglutaryl-CoA-reductase inhibitors", "reductase","inhibitors", "atrial fibrillation", "Atrial Fibrillation/drug therapy", "Atrial Fibrillation/prevention and control", "effectiveness"[All Fields], and "treatment outcome"*. The search was limited to include only English- and Danish-language studies in humans. Additional studies were identified from the reference lists of the publications selected in the search.

1.12.1 Antiplatelets

Three recent Chinese publications investigated the effectiveness of secondary prophylaxis with antiplatelet therapy.[86-88] Two studies performed by Ding et al (2009 and 2010) included the same patient population. They followed 1951 patients diagnosed with acute ischemic stroke for one year after hospital admission, and 78.2% of the patients routinely received antiplatelet therapy. In the 2009 study, antiplatelet therapy was associated with a lower risk of all-cause deaths and recurrent cerebrovascular events following ischemic stroke, with adjusted hazard ratios (HR) of 0.42 (95%CI: 0.21-0.86) and 0.58 (95%CI: 0.36-0.92), respectively.[86] The 2010 study examined the association between antiplatelet therapy and the risk of further vascular events (TIA, hemorrhagic stroke, stable/unstable angina, myocardial infarction, or peripheral arterial disease). They found an adjusted HR of 0.52 (95%CI: 0.35-0.77).[87] It is important to note that both studies had incomplete follow-ups and excluded vascular events that occurred within one month of stroke onset; thus, they most likely underestimated the vascular event rates, because recurrent stroke is most common during the early period after an initial stroke. The third study, by Kong et al, investigated, among other things, sex-related differences in effectiveness of antiplatelet therapy among 2774 patients with ischemic stroke.[88] In that study, antiplatelet therapy was associated with a reduced risk of death within one year after stroke in women (adjusted HR=0.55, 95%CI: 0.37-0.83, with no treatment as a reference), but they did not find the association in men (estimate not presented in the paper).

1.12.2 Anticoagulants

The effectiveness of anticoagulant therapy appears only to have been investigated in primary stroke prophylaxis.[82, 89-96] Caro et al (1999) studied 221 patients with AFLI, and found that oral anticoagulant therapy reduced the risk of stroke by 69%.[89] Aronow et al (1999) studied 312 patients with chronic AFLI. They found that oral anticoagulants reduced the risk of stroke by 76%.[90] A larger Danish study by Frost et al (2002) included 5124 patients with atrial fibrillation or flutter.[91] That study found that the adjusted RR of stroke associated with use of oral anticoagulants compared to no use were 0.6, 95%CI: 0.4-1.0 in men and 1.0, 95%CI: 0.7-1.6 in women. However, they also found that the estimates varied with age in men, but not in women; i.e., in men aged 60-74 and 75-89, the adjusted RRs were 0.5 (95%CI: 0.3-0.9) and 0.9 (95%CI: 0.4-1.8), respectively.[91] Therefore, the apparent sex-related differences in the effectiveness of oral anticoagulants were actually caused by age-related differences in effectiveness. A later study by Go et al (2003) included 11 526 patients with nonvalvular AFLI. They found that, compared with no warfarin treatment, warfarin treatment was associated with a 51% (95%CI: 39%-60%) lower risk of thromboembolism, of which most were ischemic strokes, and with a reduced risk of all-cause mortality (HR=0.69, 95%CI: 0.61-0.77), after adjustment for differences in age, sex, and known risk factors for stroke. An additional analysis, performed as a nested case-control study within this population, showed that warfarin was effective in reducing thromboembolic risk in the presence or absence of risk factors for stroke; there was a 64% reduction in the odds of thromboembolism with warfarin treatment compared to no antithrombotic treatment. Likewise, a study performed by Darkow et al (2005) examined warfarin utilization and clinical effectiveness among 12 539 patients with nonvalvular AFLI within usual clinical care in a managed care system.[93] Darkow et al measured the occurrence of thromboembolism, ischemic stroke, and hemorrhage in patients eligible for warfarin treatment that received therapy compared to those eligible that did not receive warfarin. They found that the adjusted risks for ischemic stroke and any thromboembolism were significantly reduced by 22% (HR=0.78, 95%CI: 0.65-0.93) and 34% (HR=0.66, 95%CI: 0.59-0.75), respectively. Their results differed from those of Go et al, because they found no increased risk of intracranial hemorrhage or other major bleeding that would lead to acute hospitalization among users of warfarin after adjustment (HR=0.97, 95%CI: 0.82-1.15).[93] Birman-Deych et al (2006) performed a US study that included 16 007 Medicare beneficiaries with AFLI. The primary outcome was hospitalization due to ischemic stroke. Among patients with AFLI that were eligible

for anticoagulant therapy, two thirds were prescribed warfarin treatment. They found that, after adjustments, warfarin treatment was associated with 35% fewer ischemic strokes (HR=0.65, 95%CI: 0.55-0.76) compared to no treatment.[94] This finding was supported in another US study by Lakshminarayan et al (2006) that included an annual 5% sample of Medicare patients aged ≥65 years from 1992 to 2002. In that study, annual trends indicated that, as the rate of warfarin use increased, the rate of ischemic stroke decreased, with no change in hemorrhagic stroke rates.[95] In a Canadian study, Parkash et al (2007) investigated the effectiveness of warfarin in 425 patients with AFLI from 1999 to 2001. They found that the annual rate of ischemic strokes was 1.2% with warfarin treatment compared to 3.1% without warfarin treatment. This represented a RR reduction of 62% (OR=0.29, 95%CI: 0.08-1.04).[96] Although the overall rate of major bleeding in the study population was 2.6% and 1.4% with and without warfarin treatment, respectively, the difference was not statistically significant (*P*=0.667). Finally, a study by Fang et al (2005) showed that warfarin reduced the rate of thromboembolisms (93.7% of which were ischemic strokes) at least as effectively, if not more, in women as in men (RR=0.4, 95%CI: 0.3-0.5 and RR=0.6, 95%CI: 0.5-0.8, respectively).[82]

1.12.3 Antihypertensives

The effectiveness of antihypertensive therapy appears mainly to have been examined in primary stroke prophylaxis [97, 98], with the exception of a study by Kong et al (2010).[88] Kong et al also studied the relationship between the effectiveness of secondary antihypertensive stroke prophylaxis and mortality. In that study, the antihypertensive treatment was associated with a reduction in the HR for death at one year in women after adjustment (HR=0.61, 95%CI: 0.42-0.90, with no treatment as a reference).[88] In an unadjusted analysis, this association was also indicated for men (HR=0.64 95%CI: 0.44-0.91). However, the study did not distinguish between various types of antihypertensive treatments. The remaining studies examined primary prophylaxis with antihypertensives. A US study by Klungel et al (2001) included 3170 enrollees of the Group Health Cooperative of Pudget Sound (380 ischemic stroke cases and 2790 hypertensive controls). They investigated associations between first ischemic stroke and different antihypertensive drugs.[97] They found that, among single drug therapies, the risk of ischemic stroke was increased 2.03 to 2.79-fold with beta blockers, calcium blockers, or ACE inhibitors compared to a thiazide diuretic alone. Also, combinations of antihypertensive drugs that did not include a thiazide diuretic were

associated with an increased risk of ischemic stroke compared to a regimen that included a thiazide.[97] In a Canadian study that included 339 patients with acute ischemic stroke, Yu et al (2009) found a similar association in pre-hospital treatments with a non-thiazide diuretic drug.[98] In that study, ATII antagonists were associated with increased initial stroke severity, as measured by the Canadian Neurological scale (OR=2.13 95%CI: 1.00-4.52). For overall pre-stroke antihypertensive therapy, the study displayed a trend towards increased initial stroke severity and poor outcome at 10 days after stroke associated with use; but those results were not statistically significant.[98]

1.12.4 Statins

Statins have mainly been examined for effectiveness in primary prophylaxis for stroke; however two recent studies focused on the effectiveness of statins in secondary prophylaxis in stroke patients.[87, 99] Of the latter, one was the study by Ding et al (2010) that also investigated antiplatelet therapy. In that study, statin therapy displayed a trend towards preventing new vascular events, after adjustment, in patients admitted with ischemic stroke. However, the results were not significant (HR=0.86, 95%CI: 0.53-1.38).[87] The second study, by Lingsma et al (2010), included 751 patients admitted with TIA or ischemic stroke.[99] In that study, statins showed a beneficial effect on the occurrence of vascular events within 3 years of a stroke, after adjustment for differences between statin and non-statin users, although the association was not statistically significant (OR=0.8, 95%CI: 0.6-1.2). However, they found poor adherence to statin treatment in their study, which; they speculated is why their results do not resemble those reported in clinical trials more.[99]

In summary, only a few studies have investigated the effectiveness of medical prophylactic treatment in relation to stroke, and even fewer studied secondary medical prophylaxis. The results from studies on secondary medical prophylaxis in patients with stroke indicated an association between antiplatelet therapy and reduced risks of new ischemic stroke, new vascular events, and death. Statin treatment also displayed a trend towards a beneficial effect, but not to the level seen in clinical trials and not proven statistically significant. Anticoagulant therapy for primary prophylaxis appeared to be effective in reducing the risk of ischemic stroke, other thromboembolisms, and death in patients with AFLI. Antihypertensive treatments for primary stroke prevention, other than thiazide diuretics, increased the risk of ischemic stroke events, but

thiazide diuretics appeared to reduce the risk of ischemic stroke. However, the results should be interpreted with caution, because many of the studies were small, had incomplete follow-up, or lacked detailed information on patient prognostic factors; moreover, some studies used inclusion criteria or study populations that might reduce their external validity. Thus, more studies are needed on the effectiveness of secondary medical prophylaxis in patients with stroke.

Table 3 Overview of discussed effectiveness related studies

Stage of prophylaxis	Author, year, country	N	Study design	Drugs investigated	Outcome	Conclusions
Primary						
	Caro *et al.* 1999, Canadian.[89]	221	Follow-up study	Warfarin antiplatelets and a combination of the two	Stroke and TIA	The relative effect of warfarin in preventing stroke was equivalent of than in randomized trials, although this study population was older and sicker.
	Aronow *et al*.1999, USA.[90]	312	Follow-up study	Warfarin, antiplatelets.	Ischemic stroke	Patients treated with oral anticoagulants had a significantly lower incidence of ischemic stroke than patients treated with oral antiplatelets.
	Frost *et al*. Denmark, 2002.[91]	5 124	Follow-up study	Warfarin	Stroke	Effectiveness of oral anticoagulant therapy in clinical practice may be lesser than the efficacy of oral anticoagulation reported from randomized trials.
	Go *et al*. 2003, USA.[92]	11 526	Follow-up study	Warfarin	Ischemic stroke, peripheral embolism,	Warfarin is very effective for preventing ischemic stroke in patients with

					hemorrhage and death.	AFLI in clinical practice, while the absolute increase in the risk of intracranial hemorrhage is small.
	Darkow *et al*. 2005, USA.[93]	12 539	Follow-up study	Warfarin	Ischemic stroke, thromboembolism and hemorrhage.	Warfarin is effective in reducing the risk of ischemic stroke in usual clinical care, however to a lesser degree than indicated in the efficacy achieved in clinical trials.
	Birman-Deych *et al.* 2006,USA.[94]	16 007	Follow-up study	Warfarin	Ischemic stroke	Overall, warfarin use was associated with fewer ischemic strokes compared with no antithrombotic therapy.
	Lakshminarayan *et al*. 2006, USA[95]	Varying each year from 1992 to 2002. Stroke rates computed for each year	Follow-up study	Warfarin (identified by surrogate measure)	Ischemic and hemorrhagic stroke	A protective association between use of warfarin and ischemic stroke rates was found in the study population.
	Parkash *et al*. Canada, 2007[96]	425	Follow-up study	Warfarin	Thromboembolic events including ischemic stroke	Warfarin use reduced the rate of ischemic stroke and other thromboembolic events
	Fang *et al*. 2005, USA.[82]	13 559	Follow-up study	AFLI	Mortality and AFLI related	Women are at higher risk for AFLI related

					thromboembolism including ischemic stroke.	thromboembolism off warfarin than men. Warfarin therapy appears to be at least as effective in women as in men.
	Klungel *et al.* 2001, USA[97]	Cases (380), controls (2790)	Case-control study	Antihypertensives (beta-blocker, Calcium blocker, ACE-inhibitor, thiazide)	Ischemic stroke	Antihypertensive drug regimens that did not include thiazide diuretic were associated with an increased risk of ischemic stroke compared to regimens that included thiazide.
	Yu *et al*. 2009, Canada[98]	339	Retrospective follow-up study	Antiplatelets, antihypertensives, statins	Stroke severity at hospitalization and functional outcome (modified Rankin scale) at 10 days following stroke	Pre stroke use of statins or the combination of antiplatelets, antihypertensives and statins were both associated with a favorable outcome 10 days following stroke. Angiotensin II decreasing drugs were associated with increased initial stroke severity.
Secondary						
	Ding *et al.* 2009, China[86]	1951	Follow-up study	Antiplatelet therapy	All-cause death	Antiplatelet therapy was associated with a decreased risk of all-cause mortality
	Ding *et al.* 2010, China[87]	1951	Follow-up study	Antiplatelet	New stroke events	Antiplatelet therapy is

				therapy, statins	and further vascular events	associated with a lower risk of recurrent cerebrovascular events and other vascular events
	Kong *et al*. 2010, China[88]	2774	Follow-up study	Antiplatelet and antihypertensive therapy	Death one year after stroke	Suboptimal antiplatelet and antihypertensive treatment are associated with death at 1 year after stroke in women
	Lingsma *et al*. 2009, Netherland[99]	751	Follow-up study	Statin	New stroke, myocardial infarction or death	Despite poor adherence to statin treatment, a beneficial effect of statin use on occurrence of vascular events within three years was observed, although not significant.

2. Aims

To examine the implementation of evidence-based stroke care in Denmark, with a specific focus on possible age- and sex-related differences, the aims of the PhD project were defined as follows:

2.1 Study I:

- To determine whether there are age-related differences in quality of care during hospitalization in patients with acute stroke in Denmark
- To evaluate the possible impact of any age-related differences in quality of care on short-term mortality

2.2 Study II:

- To determine whether there are sex-related differences in quality of care during hospitalization in patients with acute stroke in Denmark
- To evaluate the possible impact of any sex-related differences in quality of care on short-term mortality

2.3 Study III:

- To determine whether there are age- and/or sex-related differences in the use of medical prophylaxis in patients with ischemic stroke following hospital discharge in Denmark
- To evaluate the possible impact of any age- and/or sex-related differences in medical prophylaxis after hospital discharge on short- and long-term mortality

2.4 Study IV:

- To examine the association between the use of medical prophylaxis following hospital discharge and clinical outcomes for patients with ischemic stroke
- To examine whether age and/or sex influenced the effectiveness of medical prophylaxis following hospitalization in patients with ischemic stroke

3. Materials and Methods

3.1 Data sources

3.1.1 The Danish National Indicator Project (DNIP)

The Danish National Health Service provides tax-supported health care to the country's 5 million residents, all of whom have free access to hospital care. The Danish National Indicator project (DNIP) is a nationwide initiative established in 2000 to monitor and improve the quality of care for specific diseases, including stroke. The monitoring of quality of care in DNIP is based on indicators that reflect specific clinical criteria for quality of care. The indicators were identified by an expert multidisciplinary group that included different clinical professions (physicians, nurses, physiotherapists, occupational therapists, and others) and represented all relevant organizations within the field, including the Danish Stroke Society, the Danish Nursing Association, etc. The indicator selection was based on the available scientific literature.[100] In the absence of scientific evidence, for clinical problems considered important in relation to the disease, indicators were determined by consensus in the expert group. Process indicators assess what the provider did for the patient, and how well he or she did it (i.e. correct diagnostic approach to symptoms). Outcome indicators asses the influence of the health care delivery process on the health of the patient (e.g., mortality). In 2003, seven process indicators and one outcome indicator were used to monitor the quality of acute stroke care in DNIP (*appendix 1).* In 2005, the timeframe was tightened for the timeliness of CT/MR diagnostics. In 2008, two more process indicators were added *(appendix 2 and 3)*. Indicators and standards have been implemented in all clinical units and departments in Denmark treating patients with stroke, and participation is mandatory. The DNIP started collecting data on stroke in January 2003; national and regional auditing processes are organized on a yearly basis to evaluate the findings and to ensure implementation of improvements. All results of the project are made publically available in order to inform the public.

3.1.2 The National Registry of Patients

The National Registry of Patients contains data on all patients discharged from public somatic hospitals in Denmark since 1977. It includes data on all admissions and discharges, with up to 20 diagnoses for each discharged patient. All diagnoses have been classified according to the Danish edition of the International Classification of Diseases, 10th edition (IDC-10), since 1994. All

diagnoses at discharge were assigned by the physician responsible for discharging the patient. Using the National Registry of Patients it is possible to construct the complete hospitalisation history for each patient.

3.1.3 The Civil Registration System

Since 1968, all Danish Citizens are assigned a unique 10-digit personal identification number at birth, which is used in all public registers. The Civil Registration System keeps a record of all changes in the vital status of all Danish Citizens, including change of address, date of emigration, and date of death. The personal identification number allows unambiguous linkage between all Danish public registers on an individual basis.

3.1.4 The Integrated database for Labour Market research

The Integrated Database for Labour Market Research, established in 1980, contains information on each Danish citizen's socioeconomic status, including data on income, employment status, educational level, and marital status. The data in the Integrated Database for Labour Market Research are based on other registries in the Statistics Denmark like the person registry and the tax authorities registry .[101] The database is maintained by the Statistics Denmark.

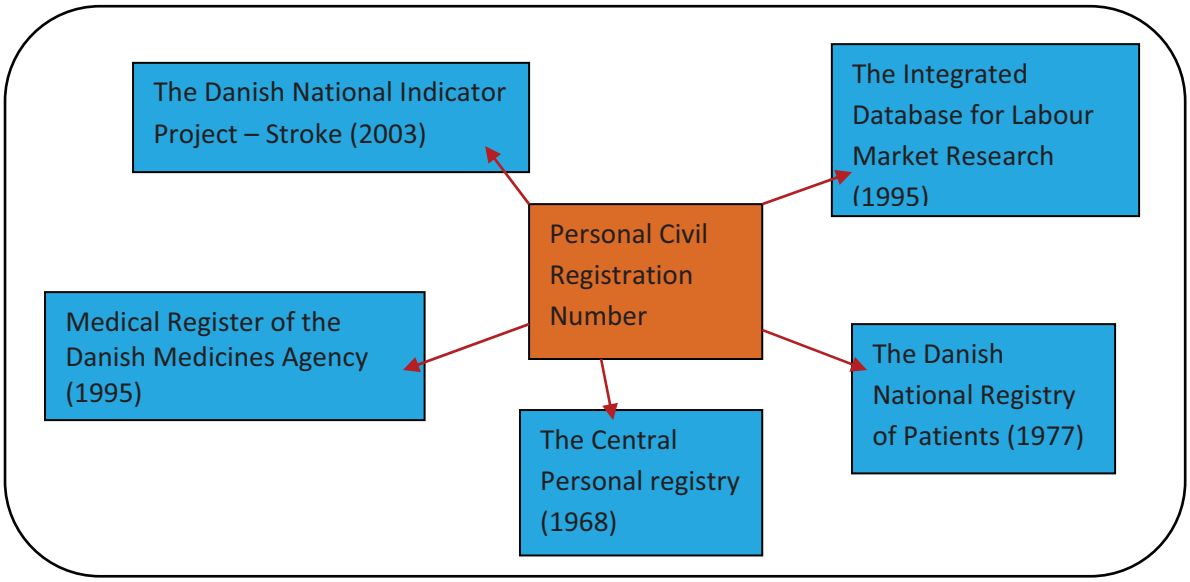
3.1.5 Medical Register of the Danish Medicines Agency

The Medical Register of the Danish Medicines Agency contains information on all filled prescriptions, including the patient's personal civil registration number, type and amount of the drug, and the date it was dispensed. From 1995 to the present, this information was collected for all prescription drugs dispensed at all Danish Pharmacies.

3.1.6. Statistics Denmark

The Statistics Denmark is a government registry subordinate to The Ministry of Economics and Business Affairs. It maintains registries of its own and compiles data from other public registries; thus, it is able to crosslink and assemble data into to specific datasets, based on the personal civil registration number. This service is available on request, once an application for a project has been approved.

Figure 2. Principle for unambiguous linkage of nationwide registries with the personal identification number.



3.2 Project design(s) and study population

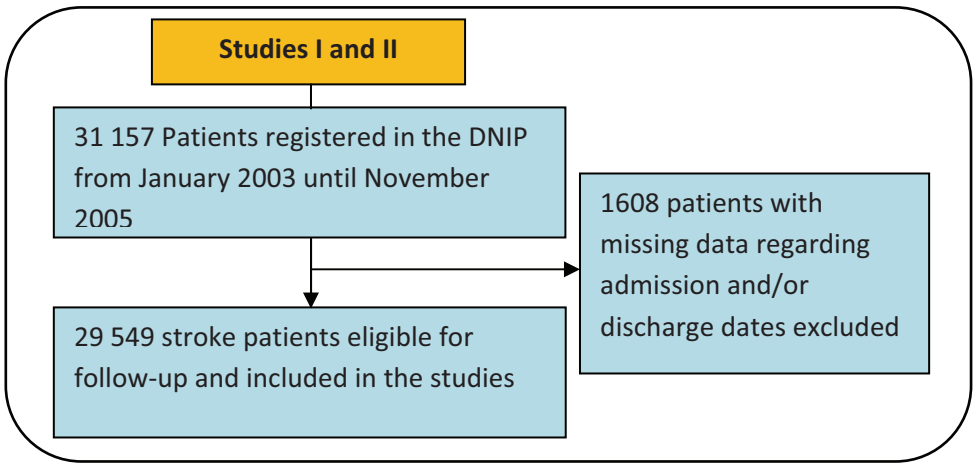
The individual studies conducted in this project were all constructed as nationwide, population-based, follow-up studies. The first two studies (I and II) examined the quality of care during hospitalization, with follow-up times that commenced at the date of hospital admission for stroke and ended on the date of death, emigration, or after 30 (or 90) days, whichever came first. The third study (III) examined the quality of secondary medical prophylaxis, with a follow-up time that commenced on day 30 after hospital discharge and ended on the date of death, emigration, or after the end of the specific follow-up period for the study, whichever came first. Study III had two follow-up periods: from 30 days to 6 months and from 12 to 18 months. The fourth study (IV) examined the effectiveness of secondary medical prophylaxis with a follow-up time that commenced on the day of hospital discharge (30 days following hospital discharge for mortality analysis) and ended on the date of death, acute myocardial infarction (AMI), recurrent stroke, emigration, or on December 31st 2007.

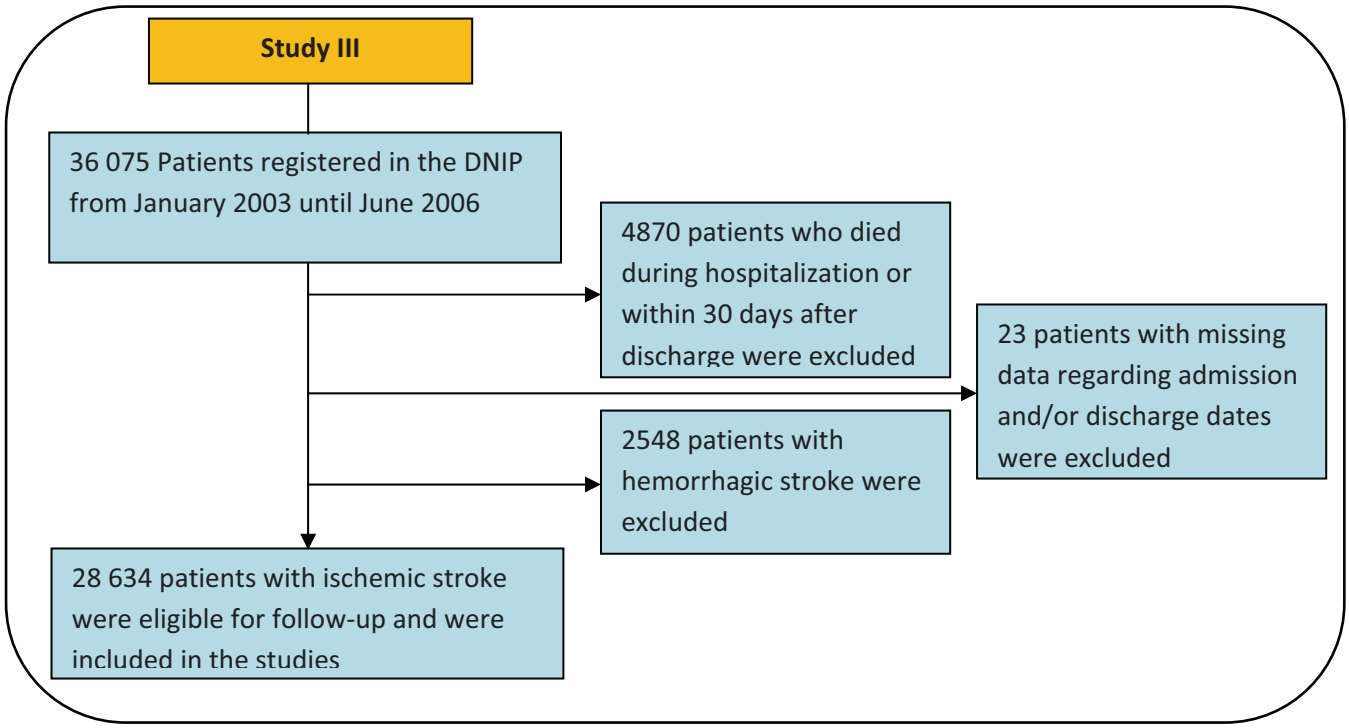
All four studies included patients admitted with acute stroke, according to the WHO criteria (i.e., rapidly developed clinical signs of focal or global disturbance of cerebral function lasting more than 24 hours or until death, with no apparent nonvascular cause[7]), which have been registered in

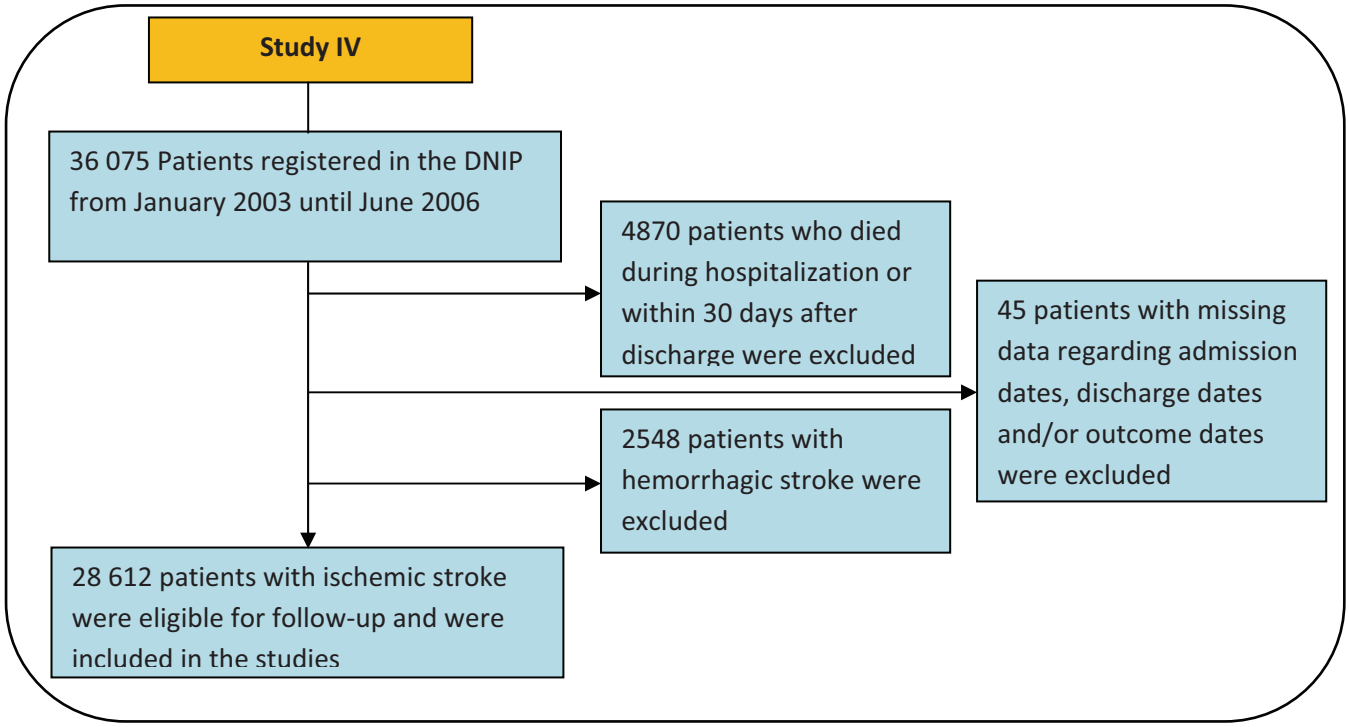
DNIP from January, 2003. The ICD-10 codes for stroke used in this project included: intracerebral hemorrhage (ICD-10 code: I61), ischemic stroke (ICD-10 code: I63), and stroke without specification (ICD-10 code: I64).

Patients were excluded when they presented with subdural hematoma, epidural or subarachnoidal hemorrhage, retinal infarct, and infarct caused by trauma, infection, surgery, or an intracerebral malignant process. Furthermore, patients were included only when they had a valid civil registration number that allowed unambiguous linkage between public registers, and when they resided in Denmark, and therefore were eligible for follow-up. Also, only the first stroke event registered in the DNIP during the study periods were included. Studies I and II included all patients (≥18 years of age) admitted to Danish hospitals with acute stroke up to November, 2005 (n=31 157). Of these patients, 29 549 were available for follow-up, and therefore, these were included in the study. Studies III and IV only included patients with ischemic stroke and stroke without specification. For those studies, we identified all patients admitted with acute stroke who were registered in the DNIP up to the end of June, 2006 (n=36 075). We excluded 4870 patients who died during hospitalization or within 30 days after hospital discharge and 2548 patients with hemorrhagic stroke. An additional 23 patients in study III and 45 patients in study IV were also excluded because they were missing information regarding admission and/or discharge dates. Data from a total of 28 634 patients in study III and 28 612 patients in study IV were available for further analyses.

Figure 3. Flow diagrams for study populations.




Study III
36 075 Patients registered in the DNIP from January 2003 until June 2006
4870 patients who died during hospitalization or within 30 days after discharge were excluded
23 patients with missing data regarding admission and/or discharge dates were excluded
2548 patients with hemorrhagic stroke were excluded
28 634 patients with ischemic stroke were eligible for follow-up and were included in the studies


Study IV
36 075 Patients registered in the DNIP from January 2003 until June 2006
4870 patients who died during hospitalization or within 30 days after discharge were excluded
45 patients with missing data regarding admission dates, discharge dates and/or outcome dates were excluded
2548 patients with hemorrhagic stroke were excluded
28 612 patients with ischemic stroke were eligible for follow-up and were included in the studies

3.3 Quality of care

3.3.1 Acute care

The measures for acute care that were used in studies I and II are process indicators registered by the DNIP (*appendix 1*). The indicators included: early admission to a specialized stroke unit, early examination with CT/MRI scan, early assessment by a physiotherapist and an occupational therapist, and early assessment of nutritional risk (*appendices 2 and 3)*. A time frame was defined for each indicator to capture the timeliness of each intervention. The time frame was the second day of hospitalization for all indicators, except early examination with CT/MRI scan, where the time frame was the first day of hospitalization (*appendices 2 and 3*). Assessment by a physiotherapist and occupational therapist was defined as a formal bed-side assessment of the patient's need for rehabilitation; assessment of nutritional risk was defined according to the recommendations of the European Society for Parenteral and Enteral Nutrition; i.e., calculation of a score that accounted for both the nutritional status and the stress induced by the stroke.[102] Patients were classified as eligible or ineligible for the specific indicators, depending on whether the stroke team or physician treating the patient had identified contraindications; e.g., rapid spontaneous recovery of motor symptoms would obviate the need for early assessments by a physiotherapist and occupational therapist. Detailed written instructions were available for the staff, which specified criteria for deeming a patient ineligible for the indicators or care processes. The reason for deeming a specific patient ineligible was not recorded in the DNIP database.

3.3.2 Secondary prophylaxis

The measures for secondary prophylaxes were different in studies I/II and studies III/IV. Studies I and II investigated in-hospital secondary medical prophylaxis with antiplatelets and oral anticoagulants registered in the DNIP database. Antiplatelet and oral anticoagulant therapies were defined as a continuous use of the drug, not merely a single dose. The time frame for these two indicators was day 2 of hospitalization for antiplatelet therapy and day 14 of hospitalization for oral anticoagulant therapy. Patients were classified as eligible or ineligible for treatment by physicians, depending on the existence of contraindications; e.g., severe dementia, active or pending hemorrhagic illnesses, risk of falling etc. Studies III and IV focused on secondary medical prophylaxis after hospital discharge and were based on data obtained from the Medical Register of the Danish Medicines Agency. All prescriptions filled by the patients from January, 2003 to the

end of December, 2007 were identified for the following drugs and their Anatomical Therapeutic Classification (ATC) codes: antiplatelet drugs (ATC B01AC), which included acetylsalicylic acid (ATC B01AC06), clopidogrel (ATC B01AC04), dipyridamol (ATC B01AC07), and combinations (ATC B01AC30); oral anticoagulants (ATC B01AA); and antihypertensives, which included ACE inhibitors or ATII antagonists (ATC C02 and C09 combined in one group), beta blockers (ATC C07), calcium antagonists (ATC C08), and thiazide diuretics (ATC C03A).

3.4 Covariates

In all four studies, we included a number of covariates in our analyses, due to their potential associations with the exposures and outcomes investigated. We included information on some or all of the following covariates: sex, age, stroke severity, diabetes, atrial fibrillation, myocardial infarction, hypertension, former stroke, intermittent claudication, Charlson comorbidity index, quality of in-hospital care, smoking, alcohol intake, type of residence, civil status, and employment status.

Employment status was based on the annual income and source of income for each individual, and it was collected from tax returns and other public registries. This data was obtained from The Integrated Database for Labour Market Research.

Data on comorbidity at the time of hospital admission or discharge was obtained from the National Registry of Patients. This information was used to compute the Charlson comorbidity index, which applies a weighting of 1, 2, 3, or 6 points to each of 19 disease categories, according to their impact on patient survival. The sum of these weights was categorized as one of three levels of comorbidity: 0 comorbidities (“none”) which applies to patients with no previously recorded diseases listed in the Charlson comorbidity index; 1–2 comorbidities (“moderate”), and >2 comorbidities (“high”). Also, for some analyses, we excluded some of the 19 disease categories from the Charlson index; instead, we adjusted for those categories as individual covariates, based on the well-established prognostic role of those conditions in stroke patients.

The remaining covariates were obtained from the DNIP, which records them at hospital admission.

3.5 Statistical analysis

Study I: We compared the proportions of patients in different age groups that received adequate care, as measured by fulfillment of the individual process indicators from the DNIP; patients ≤65 years of age were considered the reference group. The relative risks (RRs) were computed for each

age group (≤65, 65–80, and >80 years). We then used Cox Proportional Hazards regressions to compare times to death within 30 or 90 days after the stroke for different age groups, after adjusting for potential confounders of the association between age and mortality; i.e., indicators of in-hospital quality of care and prognostic factors. Analyses on the individual indicators were only performed on patients deemed eligible for the indicator in question. Multivariate analyses were adjusted for: gender, civil status, type of residence, stroke severity, former stroke, myocardial infarction, atrial fibrillation, hypertension, diabetes, intermittent claudication, smoking, and alcohol intake.

Study II: To evaluate quality of care, we first calculated, for each sex, the proportion of patients that received adequate care, defined both as fulfillment of the specific quality of care criteria and as the proportion of fulfilled criteria that the patient was deemed eligible for (<50%, 50–99%, and 100%). We further stratified the patients according to age (≤65, 65–80, and >80 years). We then compared the proportion of patients that fulfilled the criteria in each age group and computed RRs with male sex as the reference. Finally, we used Cox Proportional Hazards regressions to obtain mortality rate ratios (MRRs) for the times to death within 30 or 90 days after the stroke for the different sexes, after adjusting for potential confounders of the association between sex and mortality; i.e., patient characteristics, hospital department, and fulfillment of quality of care criteria. Adjustments were made for the following patient characteristics; age, civil status, type of residence, stroke severity, atrial fibrillation, hypertension, diabetes, intermittent claudication, Charlson comorbidity index score, smoking, and alcohol intake.

Study III: All comparisons of individual drugs were made across six age and sex groups, with males ≤65 years of age as the reference. A combination drug group was created that comprised an antiplatelet drug plus any antihypertensive drug and a statin. First, the use of medical prophylaxis was assessed by computing the proportion of patients who filled at least one prescription for a drug in the specified drug class between 0 to 6 months or 12 to 18 months after hospital discharge. Then, continued drug use was defined as the proportion of patients that survived at 18 months after discharge and had filled at least one prescription in both time windows. We then used logistic regression to perform crude and adjusted comparisons across age and sex groups. Comparisons of oral anticoagulant therapy included only patients with atrial fibrillation and

without registered contraindications for this therapy during hospital admission. Finally, we used Cox Proportional Hazards Regression to compute age- and sex-specific, crude and adjusted MRRs in the two follow-up periods. We adjusted for differences in patient characteristics, quality of in-hospital care (defined as the percentage of fulfilled indicators), 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.

Study IV: The cumulative incidence of AMI and recurrent stroke were computed after taking into account the competing risk of death. Then, Cox Proportional Hazards Regressions were used to compute drug-specific MRRs and Hazard Ratios (HRs) for AMI and recurrent stroke, with no treatment as the reference. Drug use was assessed as time-dependent variables with the start date as the date the prescription was filled, and a 90-day duration for each prescription. Thus, prescriptions that were filled within 90 days before the outcome date were considered currently in use. Multiple imputation was used to infer missing values for former stroke, former myocardial infarction, diabetes, atrial fibrillation, hypertension, intermittent claudication, Scandinavian Stroke Scale Score, smoking, alcohol consumption, type of residence at hospitalization, civil status, Charlson comorbidity index score, and percentage of indicators fulfilled during hospitalization. Five imputed data sets were generated, and the MRRs/HRs were then averaged across the five imputations, correcting for between- and within-imputation variation.[103-105] Apart from all the measured covariates, the event indicator and the Nelson-Aalen estimator of the cumulative hazard were included into the survival time in the imputation model.[106] This analysis was also performed on groups stratified by age and sex, with no treatment as the reference for each of the six strata (men or women ≤65 years, men or women 65-80 years, and men or women >80 years). Finally, we performed an additional analysis on groups stratified by propensity scores. In this analysis, patients were stratified in quartiles, according to the discharge propensity of filling prescriptions for a combination of antiplatelets, antihypertensives, and statins during the first 180 days following discharge. This analysis was included in order to overcome the potential problem of confounding by indication (i.e., patients with longer expected survival times may have been more likely to receive prescriptions for secondary medical prophylaxis).

All analyses for the project were performed with STATA® versions 9.0 and 10.1 (StataCorp LP, College Station, TX, USA).

3.6 Permissions

This project was based on data obtained from different public nation-wide registers. Therefore, patient consent to participate was not required, according to Danish law. Permissions to use and link public registers were obtained from the Danish Data Protection Agency, DNIP, and Statistics Denmark.

4. Results

4.1. Study I:

Among the 29 549 patients included in the study, increasing age was associated with a more adverse prognostic profile, including atrial fibrillation, previous myocardial infarction, and previous stroke; likewise, the proportion of patients with severe stroke increased with age.

The proportion of eligible patients who fulfilled the quality of care criteria decreased with age for all the examined processes. In all analyses, the oldest patients (>80 years) were least likely to fulfill the quality of care criteria; i.e., the relative risk (RR) for receiving specific components of care ranged from 0.66 (95% CI: 0.60–0.73) to 0.97 (95% CI: 0.95–0.99) compared to patients ≤65 years of age (Table 4). However, the RR remained above 0.90 for all quality of care criteria, except treatment with oral anticoagulants (RR=0.66, 95% CI: 0.60–0.73) and early assessment of nutritional risk (RR=0.78, 95% CI: 0.76-0.82). A total of 12 744 patients were eligible for all quality of care criteria; i.e., patients had no contraindications to any of the investigated processes of care. Age-related differences were also observed within this subgroup; 23.7%, 21.4%, and 16.5% of patients aged ≤65, >65–80, and >80 years of age, respectively, fulfilled all of the quality of care criteria.

Cumulative mortality increased with age. As expected, we found a reduction in the MRRs after adjustment for a wide range of prognostic factors. However, further adjustment for age-related differences in fulfillment of quality of care criteria had little or no effect on age-related differences in mortality (Table 5). This pattern was observed for both 30– and 90–day MRR analyses. Among the 12 744 patients who were eligible for all quality of care criteria, the age-related differences in both 30– and 90– mortality were also observed, and likewise, remained unaltered after accounting for age-related differences in fulfillment of the quality of care criteria.

Table 4. Fulfilment of quality of care criteria according to age.

Fulfilment of quality of care criteria	**≤ 65years (%)** n=8580	**RR (reference)**	**>65-80 years (%)** n=12 474	**RR (95%CI)**	**>80 years (%)** n=8495	**RR (95%CI)**
Treatment/rehabilitation in stroke unit	1954/6 576 (77.1)	1.0	2904/9 472 (76.5)	0.99 (0.98-1.01)	2124/6 308 (74.9)	0.97 (0.95-0.99)
Antiplatelet therapy	1422/4 719 (76.8)	1.0	2028/5 688 (73.7)	0.96 (0.94-0.98)	1239/2 920 (70.2)	0,91 (0,89-0,94)
Oral anticoagulant therapy	102/199 (66.1)	1.0	490/736 (60.0)	0.91 (0.82-0.99)	674/526 (43.8)	0.66 (0.60-0.73)
CT/MRI scan	1359/6 895 (83.5)	1.0	2 466/9 521 (79.4)	0.95 (0.93-0.96)	1766/6 301 (78.1)	0.93 (0.92-0.95)
Assessment by a physiotherapist	3214/3 237 (50.2)	1.0	4964/5 025 (50.3)	1.00 (0.97-1.03)	3627/3 211 (47.0)	0.94 (0.90-0.97)
Assessment by an occupational therapist	3603/2 910 (44.8)	1.0	5564/4 401 (44.2)	0.99 (0.95-1.02)	3871/2 838 (42.3)	0.95 (0.91-0.98)
Nutritional risk evaluation	2661/3 163 (54.3)	1.0	4364/4 267 (49.4)	0.91 (0.88-0.94)	3261/2 432 (42.7)	0.78 (0.76-0.82)

Table 5. Mortality rate ratios (MRR) during 30 days, according to age. Adjusted for fulfilment of quality of care criteria and prognostic factors.

Quality of care criterion	Number (n)	Age	Absolute Mortality	Crude MRR (95%CI)	Adj. MRR* (95%CI)	Fully adj. MRR† (95%CI)
Treatment/rehabilitation in Stroke unit	29 338	≤ 65	443/8530 (5.2%)	1.00	1.00	1.00
		> 65-80	1197/12 376 (9.7%)	1.90 (1.70-2.12)	1.52 (1.33-1.72)	1.52 (1.34-1.73)
		> 80	1638/8432 (19.4%)	3.97 (3.58-4.41)	2.03 (1.78-2.32)	2.05 (1.80-2.35)
Antiplatelet therapy	18 016	≤ 65	127/6141 (2.1%)	1.00	1.00	1.00
		> 65-80	319/7716 (4.1%)	2.01 (1.64-2.48)	1.57 (1.25-1.97)	1.55 (1.24-1.95)
		> 80	398/4159 (9.6%)	4.78 (3.91-5.84)	2.63 (2.07-3.34)	2.62 (2.06-3.33)
Oral anticoagulant therapy	2 727	≤ 65	10/301 (3.3%)	1.00	1.00	1.00
		> 65-80	97/1226 (7.9%)	2.43 (1.27-4.66)	2.37 (1.12-5.02)	2.27 (1.07-4.82)
		> 80	207/1200 (17.3%)	5.54 (2.94-10.45)	3.84 (1.81-8.15)	3.34 (1.57-7.12)
CT/MRI scan	28 308	≤ 65	430/8254 (5.2%)	1.00	1.00	1.00
		> 65-80	1113/11 987 (9.3%)	1.82 (1.62-2.03)	1.43 (1.26-1.63)	1.44 (1.26-1.64)

		> 80	1477/8067 (18.3%)	3.71 (3.33-4.14)	1.90 (1.66-2.18)	1.92 (1.68-2.19)
Assessment by a physiotherapist	23 277	≤ 65	184/6451 (2.9%)	1.00	1.00	1.00
		> 65-80	634/9988 (6.3%)	2.26 (1.92-2.67)	1.68 (1.41-2.02)	1.70 (1.42-2.03)
		> 80	921/6838 (13.5%)	4.95 (4.22-5.79)	2.46 (2.04-2.97)	2.48 (2.06-2.99)
Assessment by an occupational therapist	23 187	≤ 65	172/6513 (2.6%)	1.00	1.00	1.00
		> 65-80	595/9965 (6.0%)	2.30 (1.94-2.72)	1.71 (1.42-2.07)	1.72 (1.43-2.08)
		> 80	875/6709 (13.0%)	5.16 (4.38-6.08)	2.58 (2.12-3.13)	2.60 (2.15-3.17)
Nutritional risk evaluation	20 148	≤ 65	165/5824 (2.8%)	1.00	1.00	1.00
		> 65-80	532/8631 (6.2%)	2.21 (1.86-2.63)	1.61 (1.33-1.95)	1.61 (1.32-1.95)
		> 80	781/5693 (13.7%)	5.08 (4.29-6.01)	2.43 (1.99-2.97)	2.43 (1.99-2.97)

*Adjusted for prognostic factors (gender, civil status, type of residence, stroke severity, former stroke, AMI, atrial fibrillation, hypertension, diabetes, intermittent claudication, smoking and alcohol).

†Adjusted for fulfilment of the specific quality of care criterion and prognostic factors.

4.2 Study II:

Among the 29 549 patients included in the study, female sex was associated with higher proportions of older patients, atrial fibrillation, hypertension, severe strokes, convalescent/nursing home residency, and patients living alone. Male sex was associated with higher proportions of diabetes, myocardial infarction, former strokes, intermittent claudication, high alcohol intake, and daily smoking. Again, only eligible patients were included in the analysis of the individual quality of care criteria. The analyses were performed on stratified age groups, as defined in study I, with males as the reference. There were no differences in the proportions of men and women considered ineligible or with missing data for the specific quality of care criteria. The proportion of eligible patients who fulfilled the quality of care criteria was slightly lower for women compared to men, but the RR remained above 0.9 for all quality of care criteria. The RRs were predominantly statistically insignificant, except for oral anticoagulant therapy among patients aged ≤65 years (RR=0.84, 95% CI: 0.69–1.03) and those >80 years (RR=0.84, 95% CI: 0.74–0.96) (Table 6). Among the 12 744 patients who were eligible for all quality of care criteria, the age-stratified groups showed only modest sex-related differences. The largest sex-related difference was among patients 65 to 80 years old, where the RR between women and men that fulfilled 100% of the criteria was 0.90 (95% CI: 0.85–0.96). For patients ≤ 65 and >80 years old, the corresponding RRs were 0.99 (95% CI: 0.92-1.06) and 0.94 (95% CI: 0.86-1.02), respectively.

Cumulative mortality and crude MRRs were higher for women compared to men. As expected, we found a reduction in MRRs after adjustment for patient characteristics, including sociodemographic and clinical characteristics. The adjusted MRRs were 0.79 (95%CI: 0.73-0.86) for 30 day mortality and 0.81 (95%CI: 0.75-0.87) for 90 day mortality. Not surprisingly, because only modest differences in quality of care were detected between the sexes, further adjustments for differences in the proportions of fulfilled quality of care criteria had only a marginal impact on the adjusted MRRs; i.e., the fully adjusted MRRs were 0.79 (95%CI: 0.72-0.86) for 30 day mortality and 0.81 (95%CI 0.75-0.87) for 90 day mortality. Stratifying the analyses according to age did not change this pattern (Table 7). The survival advantage of female patients was also apparent when stratifying for age, particularly in the oldest age group for 30 day mortality.

Table 6. Fulfilment of quality of care criteria according to sex and stratified by age

Fulfilment of quality of care criteria	***Age***	***Male (%) (n=15 372)***	***Female (%) (n=14 177)***	**RR (95%CI)**
Treatment/rehabilitation in stroke unit	≤ 65	4233/5466 (77.4 %)	2343/3064 (76.5 %)	0.99 (0.96-1.01)
	>65-80	5173/6686 (77.4 %)	4299/5690 (75.6 %)	0.98 (0.96-1.00)
	> 80	2328/3112 (74.8 %)	3980/5320 (74.8 %)	1.00 (0.97-1.03)
Antiplatelet therapy	≤ 65	3062/3 945 (77.6 %)	1657/2 196 (75.5 %)	0.97 (0.94-1.00)
	>65-80	3207/4 243 (75.6 %)	2481/3 473 (71.4 %)	0.95 (0.92-0.97)
	> 80	1182/1 629 (72.6 %)	1738/2530 (68.7 %)	0.95 (0.91-0.99)
Oral anticoagulant therapy	≤ 65	148/214 (69.2 %)	51/87 (58.6 %)	0.84 (0.69-1.03)
	>65-80	398/647 (61.5 %)	338/579 (58.4 %)	0.95 (0.87-1.04)
	> 80	210/431 (48.7 %)	316/769 (41.1 %)	0.84 (0.74-0.96)
CT/MRI scan	≤ 65	4432/ 5296 (83.7 %)	2463/ 2958 (83.2%)	0.99 (0.98-1.01)
	>65-80	5157/ 6474 (79.7 %)	4364/ 5513 (79.2 %)	0.99 (0.98-1.01)
	> 80	2347/ 2992 (78.4 %)	3954/ 5075 (77.9 %)	0.99 (0.97-1.02)
Assessment by a	≤ 65	2119/ 4181	1118/ 2270	0.97 (0.92-1.02)

physiotherapist		(50.7 %)	(49.3 %)	
	>65-80	2809/ 5 399 (52.0 %)	2215/ 4589 (48.3 %)	0.93 (0.89-0.97)
	> 80	1231/ 2558 (48.1 %)	1980/ 4280 (46.3 %)	0.96 (0.91-1.01)
Assessment by an occupational therapist	≤ 65	1881/ 4215 (44.6 %)	1029/ 2298 (44.8 %)	1.00 (0.95-1.06)
	>65-80	2446/ 5371 (45.5 %)	1955/ 4594 (42.6 %)	0.93 (0.89-0.98)
	> 80	1084/ 2504 (43.3 %)	1754/ 4205 (41.7 %)	0.96 (0.91-1.02)
Nutritional risk evaluation	≤ 65	2040/ 3771 (54.1 %)	1123/ 2053 (54.7 %)	1.01 (0.96-1.06)
	>65-80	2375/ 4678 (50.8 %)	1892/ 3953 (47.9 %)	0.94 (0.90-0.98)
	> 80	926/ 2089 (44.3 %)	1506/ 3604 (41.8 %)	0.94 (0.88-1.00)

The varying number of patients in the different indicator groups in relation to the total amount of patients is due to the fact that not all patients were deemed relevant for the individual indicator groups by hospital staff. I.e. only 87 female patients ≤ 65 were relevant for anticoagulant therapy since they had both atrial fibrillation and ischemic stroke

Table 7. Crude and adjusted mortality rate ratios during 30 and 90 days, according to sex and stratified for age.

		30-day mortality				90 day mortality			
Age (years)	**Sex**	**Proportion of patients who died N (%)**	**Unadjusted MRR (95% CI)**	**Adjusted MRR[1] (95% CI)**	**Fully adjusted MRR[2] (95% CI)**	**Proportion of patients who died N (%)**	**Unadjusted MRR (95% CI)**	**Adjusted MRR[1] (95% CI)**	**Fully adjusted MRR[2] (95% CI)**
≤65	Male	280/5217 (5.1)	1.00 (reference)	1.00 (reference)	1.00 (reference)	346/5151 (6.3)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Female	171/2912 (5.5)	1.09 (0.90-1.32)	0.90 (0.71-1.14)	0.91 (0.72-1.16)	205/2878 (6.6)	1.06 (0.89-1.26)	0.89 (0.72-1.10)	0.90 (0.73-1.11)
>65-80	Male	618/6123 (9.2)	1.00 (reference)	1.00 (reference)	1.00 (reference)	834/5907 (12.4)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Female	592/5141 (10.3)	1.13 (1.01-1.27)	0.87 (0.76-1.00)	0.86 (0.75-0.98)	782/4951 (13.6)	1.11 (1.01-1.22)	0.85 (0.76-0.96)	0.85 (0.75-0.95)
>80	Male	590/2544 (18.8)	1.00 (reference)	1.00 (reference)	1.00 (reference)	801/2333 (25.6)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Female	1057/4304 (19.7)	1.05 (0.95-1.16)	0.72 (0.63-0.82)	0.71 (0.63-0.81)	1473/3888 (27.4)	1.08 (0.99-1.18)	0.77 (0.70-0.86)	0.77 (0.69-0.86)

1: Adjusted for patient characteristics (age, civil status, type of residence, stroke severity, atrial fibrillation, hypertension, diabetes, intermittant claudication, Charlson comorbidity index score, smoking and alcohol intake) and hospital department.

2: Adjusted for patient characteristics, hospital department and percentage of fulfilled quality of care criteria.

4.3 Study III:

Among the 28 634 patients with ischemic stroke included in this study, increasing age was associated with a more adverse prognostic profile, including more severe stroke and lower quality of in-hospital stroke care. Sex was associated with the prognostic factors identified in study II. All analyses were stratified for age and sex, with males ≤65 years old as the reference.

Figure 4 shows the proportions of patients that received each type of medical prophylaxis, stratified by age and sex; Table 8 displays the corresponding adjusted odds ratios (ORs).

Increasing age was associated with a lower proportion of patients that received antiplatelet therapy, anticoagulant therapy, statins, and combination therapy at both 0–6 months and 12–18 months after discharge (Figure 4). In contrast, no overall systematic sex-related differences were identified in the use of secondary medical prophylaxis after hospital discharge. However, between 0–6 months, women ≤65 years were less likely to receive ACE inhibitors/ATII antagonists (adjusted OR=0.74, 95%CI: 0.67–0.83), but more likely to receive thiazides (adjusted OR=1.13, 95%CI: 1.01–1.28) compared to men of the same age. The more widespread use of thiazides among women was observed in all age groups in both time windows (Table 8).

Continued drug use at 12–18 months after discharge ranged from 66.1% (thiazide therapy among males ≤65 years old) to 91.9% (antiplatelet therapy among males >65 to 80 years old). For anticoagulant therapy, ACE inhibitors/ATII antagonists, statins, and combination therapy, a decrease in continued drug use was observed with increasing age. No systematic sex-related differences in continued drug use were observed (data not shown).

Age- and sex-specific cumulative mortality rates and MRRs for 30 days to 6 months and for 12–18 months are presented in Table 9. As expected, we found a reduction in MRRs after adjustment for clinical, sociodemographic, and socioeconomic characteristics. Further adjustment for the use of secondary medical prophylaxis was associated with even lower MRRs for patients >80 years of age (likelihood ratio test: $P<0.001$).

Figure 4. . Proportions of Patients Receiving Medical Prophylaxis after Hospital Discharge by Age and Sex

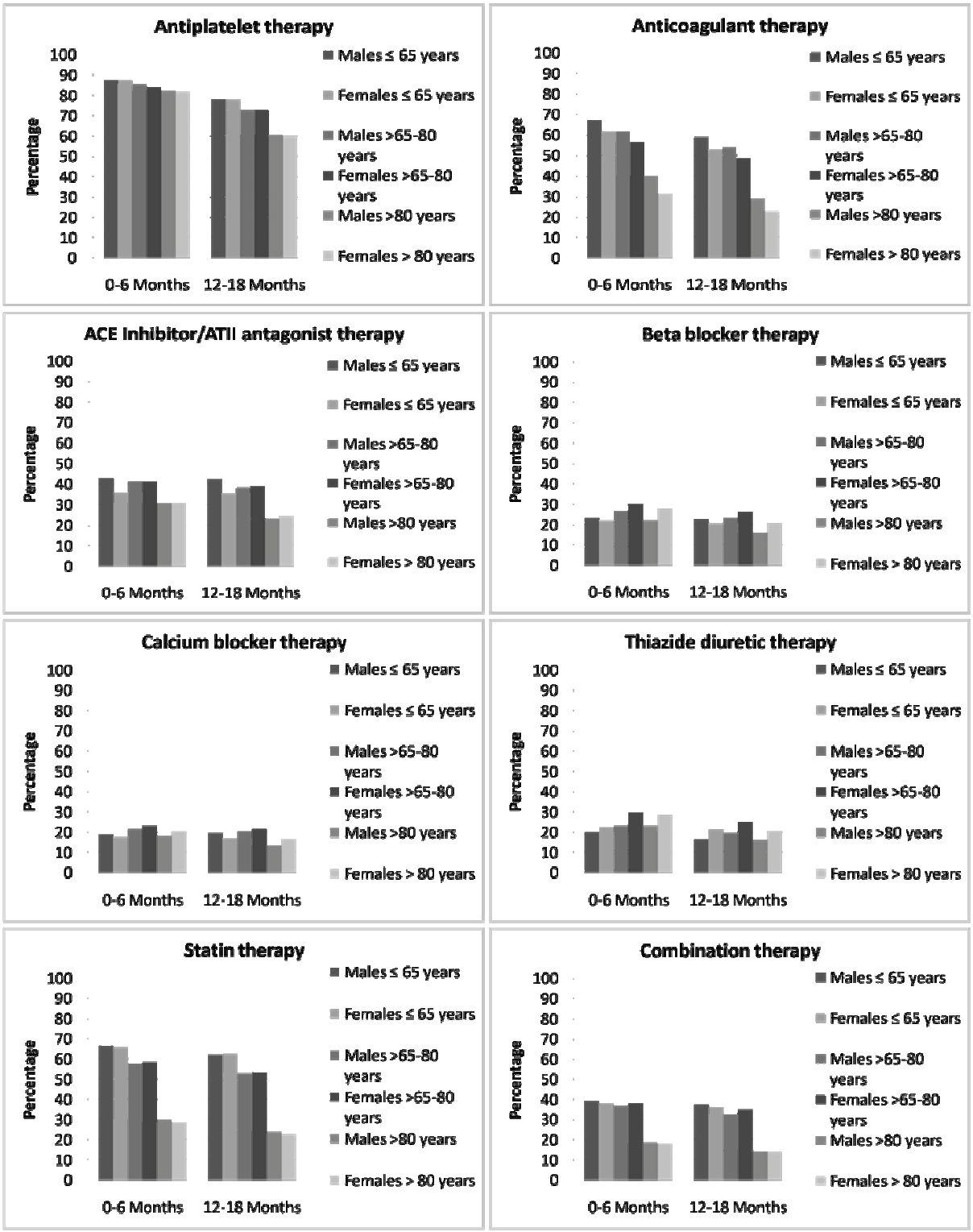


Table 8. Adjusted Odds Ratios (OR) for Medical Prophylaxis after Hospital Discharge by Age and Sex Among Patients with Ischemic Stroke

	Adjusted OR 0–6 months* (95% CI) (n=24 179)	Adjusted OR 12–18 months* (95% CI) (n=21 017)
Antiplatelets		
Males ≤65 years	1.00	1.00
Females ≤65 years	1.10 (0.95-1.29)	1.00 (0.88-1.13)
Males >65–80 years	1.01 (0.83-1.23)	1.08 (0.90-1.30)
Females >65–80 years	1.02 (0.83-1.26)	1.03 (0.85-1.26)
Males >80 years	1.07 (0.84-1.35)	1.14 (0.91-1.43)
Females >80 years	1.19 (0.94-1.49)	1.16 (0.93-1.44)
Oral anticoagulants†	*N=3537 pt*	*n=2718*
Males ≤65 years	1.00	1.00
Females ≤65 years	1.05 (0.56-1.96)	0.90 (0.51-1.59)
Males >65–80 years	0.77 (0.42-1.42)	1.07 (0.59-1.95)
Females >65–80 years	0.67 (0.36-1.24)	0.74 (0.40-1.37)
Males >80 years	0.42 (0.22-0.79)	0.46 (0.24-0.88)
Females >80 years	0.45 (0.24-0.85)	0.56 (0.29-1.06)
ACE inhibitors/ATII antagonists		
Males ≤65 years	1.00	1.00
Females ≤65 years	0.74 (0.67-0.83)	0.75 (0.68-0.84)
Males >65–80 years	0.87 (0.75-1.01)	0.88 (0.76-1.02)
Females >65–80 years	0.87 (0.75-1.02)	0.89 (0.76-1.04)
Males >80 years	0.63 (0.53-0.76)	0.57 (0.47-0.69)
Females >80 years	0.62 (0.52-0.74)	0.58 (0.49-0.70)

Beta blockers		
Males ≤65 years	1.00	1.00
Females ≤65 years	0.97 (0.86-1.10)	0.94 (0.84-1.07)
Males >65–80 years	0.88 (0.75-1.03)	0.87 (0.73-1.02)
Females >65–80 years	1.10 (0.93-1.30)	1.07 (0.90-1.27)
Males >80 years	0.61 (0.50-0.74)	0.62 (0.50-0.76)
Females >80 years	0.88 (0.73-1.06)	0.91 (0.75-1.11)
Calcium blockers		
Males ≤65 years	1.00	1.00
Females ≤65 years	0.91 (0.80-1.04)	0.85 (0.75-0.97)
Males >65–80 years	0.97 (0.82-1.15)	0.99 (0.84-1.17)
Females >65–80 years	1.03 (0.86-1.23)	1.06 (0.89-1.27)
Males >80 years	0.81 (0.66-0.99)	0.78 (0.63-0.96)
Females >80 years	0.99 (0.81-1.20)	1.02 (0.84-1.25)
Thiazide diuretics		
Males ≤65 years	1.00	1.00
Females ≤65 years	1.13 (1.01-1.28)	1.36 (1.20-1.53)
Males >65–80 years	0.98 (0.84-1.15)	1.12 (0.94-1.32)
Females >65–80 years	1.23 (1.04-1.46)	1.39 (1.17-1.67)
Males >80 years	1.06 (0.88-1.28)	1.15 (0.94-1.42)
Females >80 years	1.27 (1.06-1.53)	1.43 (1.18-1.75)
Statins		
Males ≤65 years	1.00	1.00
Females ≤65 years	1.00 (0.90-1.11)	1.02 (0.92-1.14)
Males >65–80 years	0.96 (0.83-1.10)	1.00 (0.86-1.16)
Females >65–80 years	1.23 (1.05-1.43)	1.24 (1.06-1.45)
Males >80 years	0.37 (0.31-0.44)	0.39 (0.32-0.46)
Females >80 years	0.46 (0.38-0.54)	0.47 (0.39-0.56)

Combination therapy (antiplatelet, antihypertensive,[‡] & statin)		
Males ≤65 years	1.00	1.00
Females ≤65 years	1.00 (0.90-1.11)	0.99 (0.89-1.10)
Males >65–80 years	0.93 (0.81-1.08)	0.92 (0.79-1.06)
Females >65–80 years	1.18 (1.01-1.38)	1.19 (1.02-1.40)
Males >80 years	0.45 (0.38-0.54)	0.44 (0.37-0.54)
Females >80 years	0.52 (0.43-0.62)	0.52 (0.43-0.62)

* 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.

[†] Only includes patients with atrial fibrillation and no contraindications for anticoagulant therapy during hospital admission.

Table 9. Cumulative Mortality Rates and Mortality Rate Ratios (MRR) 1–6 and 12–18 Months after Hospital Discharge Among Patients with Ischemic Stroke

		1–6 months				12–18 months			
Age	**Sex**	**Proportion of patients who died n (%)**	**Unadjusted MRR (95% CI) N=28 632**	**Adjusted MRR* (95% CI) n=24 179**	**Fully adjusted MRR† (95%CI) n=24 179**	**Proportion of patients who died n (%)**	**Unadjusted MRR (95% CI) n=25 532**	**Adjusted MRR* (95% CI) n=21 662**	**Fully adjusted MRR† (95%CI) n=21 662**
≤65	Males	101/5 751 (1.76)	1.00 (reference)	1.00 (reference)	1.00 (reference)	63/5 537 (1.14)	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)	35/3 170 (1.10)	0.97 (0.64-1.47)	0.89 (0.57-1.40)	0.95 (0.60-1.50)
>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)	200/5 967 (3.35)	2.99 (2.25-3.97)	1.86 (1.14-3.04)	1.99 (1.21-3.25)
	Females	294/5 530 (5.32)	3.08 (2.46-3.86)	1.50 (1.00-2.25)	1.58 (1.05-2.37)	147/5 044 (2.91)	2.59 (1.93-3.48)	1.67 (1.00-2.79)	1.88 (1.13-3.14)
>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)	173/2 157 (8.02)	7.35 (5.51-9.81)	4.11 (2.43-6.95)	3.40 (2.01-5.74)
	Females	617/ 4 656 (13.25)	8.02 (6.50-9.90)	2.87 (1.90-4.34)	2.63 (1.74-3.97)	253/3 657 (6.92)	6.34 (4.81-8.35)	3.53 (2.08-5.98)	3.23 (1.91-5.47)

*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)

†Additionally adjusted for use of antiplatelets, ACE-inhibitors/ATII antagonists, beta blockers, calcium blockers, thiazide diuretics and statins.

4.4 Study IV:

During the entire study period of 60 months, we recorded 7462 deaths, 837 AMIs, and 2658 recurrent stroke events in the entire study population. Figure 5 shows the cumulative incidence of death, AMI, and recurrent stroke for the 28 612 patients with ischemic stroke. The maximum observation time was five years, and the competing risk of death was taken into account in calculating the cumulative incidence of AMI and recurrent stroke. The cumulative incidence at five years after hospital discharge was 37.6% (95%CI 36.1–39.3) for death, 3.9% (95%CI 3.5%–4.4%) for AMI, and 11.7% (95%CI 10.9%–12.5%) for recurrent stroke events.

Table 10 displays the crude and adjusted relative risk estimates for death, AMI, and recurrent stroke for patients treated with the different drug classes. The overall adjusted MRRs ranged from 0.36–0.85 for treatment compared to no treatment for the seven drugs examined. All estimates were statistically significant (Table 10). Antiplatelet therapy was effective in preventing death for all age and sex groups, but the effectiveness appeared to decrease with increasing age; thus, the adjusted MRRs for men and women ≤65 years were 0.45 (95%CI: 0.38–0.53) and 0.58 (95%CI: 0.44–0.76), respectively, but the adjusted MRRs for men and women >80 years were 0.80 (95%CI: 0.71–0.90) and 0.83 (95%CI: 0.75-0.90), respectively. In contrast, the effectiveness of oral anticoagulant therapy appeared to increase with increasing age. The adjusted MRRs were 0.70 (95%CI: 0.35–1.35) and 0.78 (95%CI: 0.31-1.96) in men and women ≤65 years, respectively, compared to 0.41 (95%CI: 0.30–0.55) and 0.35 (95%CI: 0.28–0.45) in men and women >80 years, respectively. All the remaining prophylactic drugs were associated with a lower mortality after stratification for age and sex. However, the estimates for beta blocker therapy and thiazide diuretics did not reach statistical significance for all age and sex groups (data not shown). In the analysis of patients stratified by propensity score, the MRRs in the four different strata ranged from 0.40 (95%CI: 0.36–0.46) to 0.94 (95%CI: 0.87–1.01) for all drugs, with the lowest MRRs in the strata that had the highest propensity scores. For beta blockers, there were no significant changes in MRR estimates within each stratum (data not shown).

The overall adjusted HRs for AMI ranged from 0.80–1.39 for prophylaxis compared to no prophylaxis for all seven drugs examined, but only treatment with beta blockers, thiazide diuretics, and statins displayed significant effects. Although not all were statistically significant, all the examined drugs displayed HRs below 1.00 for AMI in patients with ischemic stroke, except beta

blockers and calcium blockers (Table 10). Only prophylaxes with thiazide diuretics and statins were associated with statistically significant lower risks of AMI after discharge. Overall, the adjusted age- and sex-stratified analyses displayed a similar pattern, with only very small differences between age and sex groups (data not shown). In the analyses of stratified propensity scores, the HRs ranged from 0.81 (95%CI: 0.60–1.08) to 1.34 (95%CI: 1.03–1.73). No systematic pattern was observed since for four drug groups (antiplatelets, oral anticoagulants, ACE inhibitors/ATII antagonists and beta blockers) as the lowest risk estimates were found in the strata with the highest propensity scores, whereas the opposite pattern was found among the remaining three drug groups (calcium blockers, thiazide diuretics and statins) (data not shown).

The overall adjusted HRs for recurrent stroke ranged from 0.58–1.14 for prophylaxis compared to no prophylaxis with the seven drugs examined (Table 10). Oral anticoagulants and statins were associated with the lowest risks of recurrent stroke, with adjusted HRs of 0.58 (95%CI: 0.46–0.73) and 0.84 (95%CI: 0.77-0.91), respectively. In contrast, the use of beta blockers and thiazide diuretics were associated with an increased risk of recurrent stroke, with adjusted HRs of 1.13 (95%CI: 1.02–1.24) and 1.14 (95%CI: 1.03–1.26), respectively. The analyses adjusted by stratifying for age and sex displayed a similar overall effect of treatment with the different drugs, displaying only minor differences across the age- and sex- strata (data not shown). Similarly, no systematic differences were found in the propensity score stratified analysis.

Figure 5. Cumulative Incidences with confidence intervals (CI) of death, acute myocardial infarction and recurrent stroke following hospital discharge among 28 612 patients with ischemic stroke from January 2003 till end December 2007.

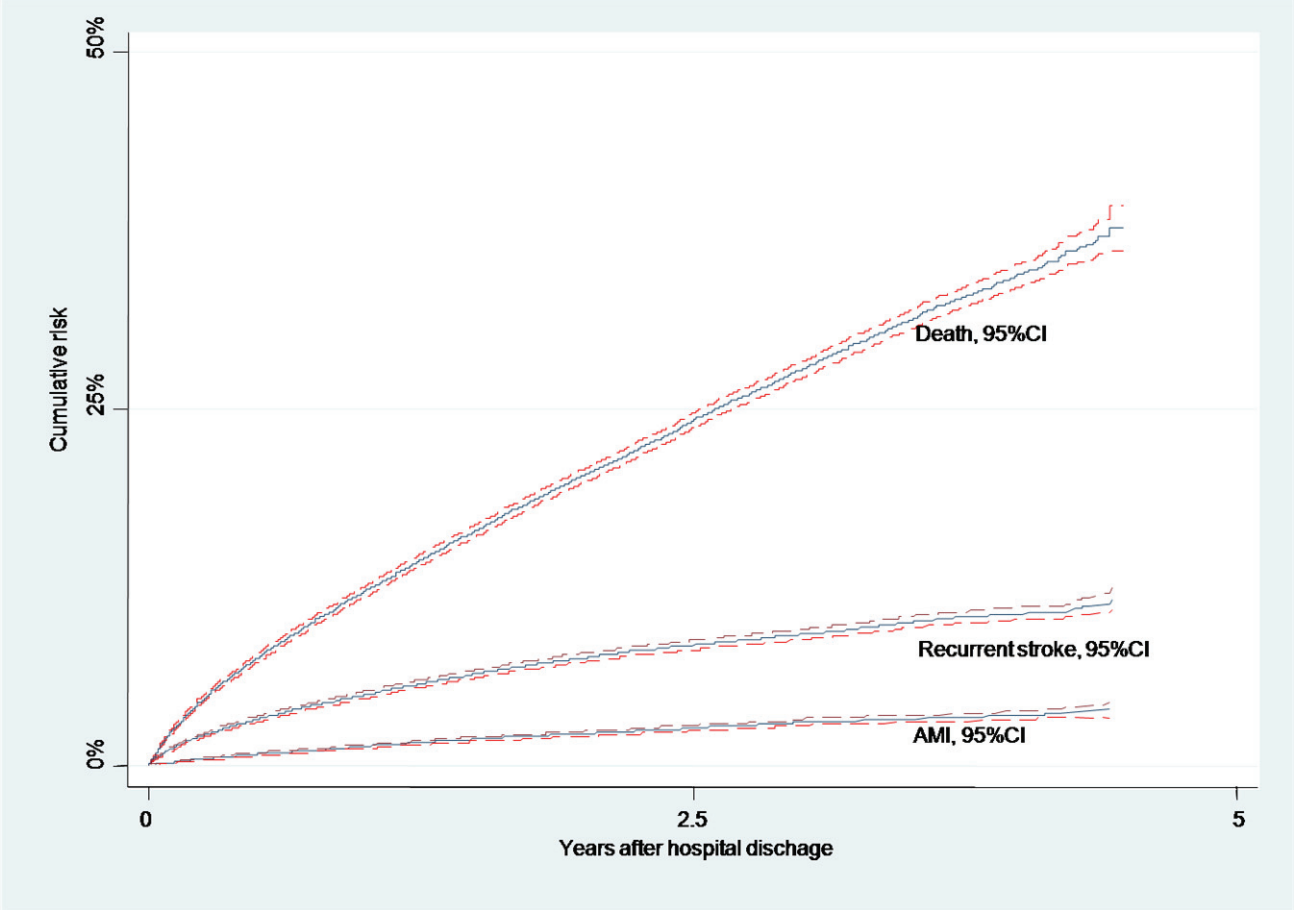


Table 10. Crude and adjusted risk of death, AMI and recurrent stroke according to use of secondary medical prophylaxis.

		N	Death Crude (HR 95% CI)	Death Adjusted (HR 95% CI)†	N	AMI Crude (HR 95% CI)	AMI Adjusted (HR 95% CI)	N	New stroke Crude (HR 95% CI)	New stroke Adjusted (HR 95% CI)
Antiplatelets										
	No	3134	1.00 (ref)	1.00 (ref)	3232	1.00 (ref)	1.00 (ref)	3488	1.00 (ref)	1.00 (ref)
	Yes	25 478	0.65 (0.62-0.68)	0.74 (0.71-0.78)	25 380	0.96 (0.82-1.13)	0.98 (0.83-1.15)	25 124	1.03 (0.94-1.12)	1.05 (0.96-1.15)
Oral anticoagulants*										
	No	1989	1.00 (ref)	1.00 (ref)	2002	1.00 (ref)	1.00 (ref)	2029	1.00 (ref)	1.00 (ref)
	Yes	2185	0.28 (0.25-0.32)	0.36 (0.32-0.41)	2172	0.73 (0.52-1.03)	0.78 (0.55-1.12)	2145	0.56 (0.45-0.69)	0.58 (0.46-0.73)
ACE Inhibitors/ATII antagonists										
	No	15 179	1.00 (ref)	1.00 (ref)	15 348	1.00 (ref)	1.00 (ref)	15 549	1.00 (ref)	1.00 (ref)
	Yes	13 433	0.66 (0.62-0.69)	0.67 (0.64-0.71)	13 264	1.14 (0.99-1.32)	0.93 (0.80-1.08)	13 063	1.00 (0.92-1.09)	0.94 (0.86-1.02)
Beta blockers										
	No	19 345	1.00 (ref)	1.00 (ref)	19 657	1.00 (ref)	1.00 (ref)	19 607	1.00 (ref)	1.00 (ref)
	Yes	9267	0.98 (0.92-1.04)	0.85 (0.80-0.90)	8955	1.84 (1.58-2.13)	1.39 (1.18-1.62)	9005	1.22 (1.11-1.34)	1.13 (1.02-1.24)
Calcium Blockers										
	No	20 538	1.00 (ref)	1.00 (ref)	20 630	1.00 (ref)	1.00 (ref)	20 821	1.00 (ref)	1.00 (ref)
	Yes	8074	0.78 (0.73-0.83)	0.75 (0.70-0.80)	7982	1.27 (1.06-1.50)	1.05 (0.88-1.26)	7791	1.08 (0.98-1.20)	1.00 (0.90-1.12)
Thiazide Diuretics										
	No	18 973	1.00 (ref)	1.00 (ref)	19 044	1.00 (ref)	1.00 (ref)	19 296	1.00 (ref)	1.00 (ref)

	Yes	9639	0.77 (0.73-0.83)	0.82 (0.77-0.88)	9568	0.79 (0.65-0.96)	0.79 (0.65-0.97)	9316	1.15 (1.03-1.27)	1.14 (1.03-1.26)
Statins										
	No	11 354	1.00 (ref)	1.00 (ref)	11 546	1.00 (ref)	1.00 (ref)	11 837	1.00 (ref)	1.00 (ref)
	Yes	17 258	0.35 (0.32-0.37)	0.41 (0.39-0.44)	17 066	0.86 (0.75-0.99)	0.80 (0.69-0.92)	16 775	0.84 (0.77-0.91)	0.84 (0.77-0.91)

* Patients with known atrial fibrillation during hospitalization only

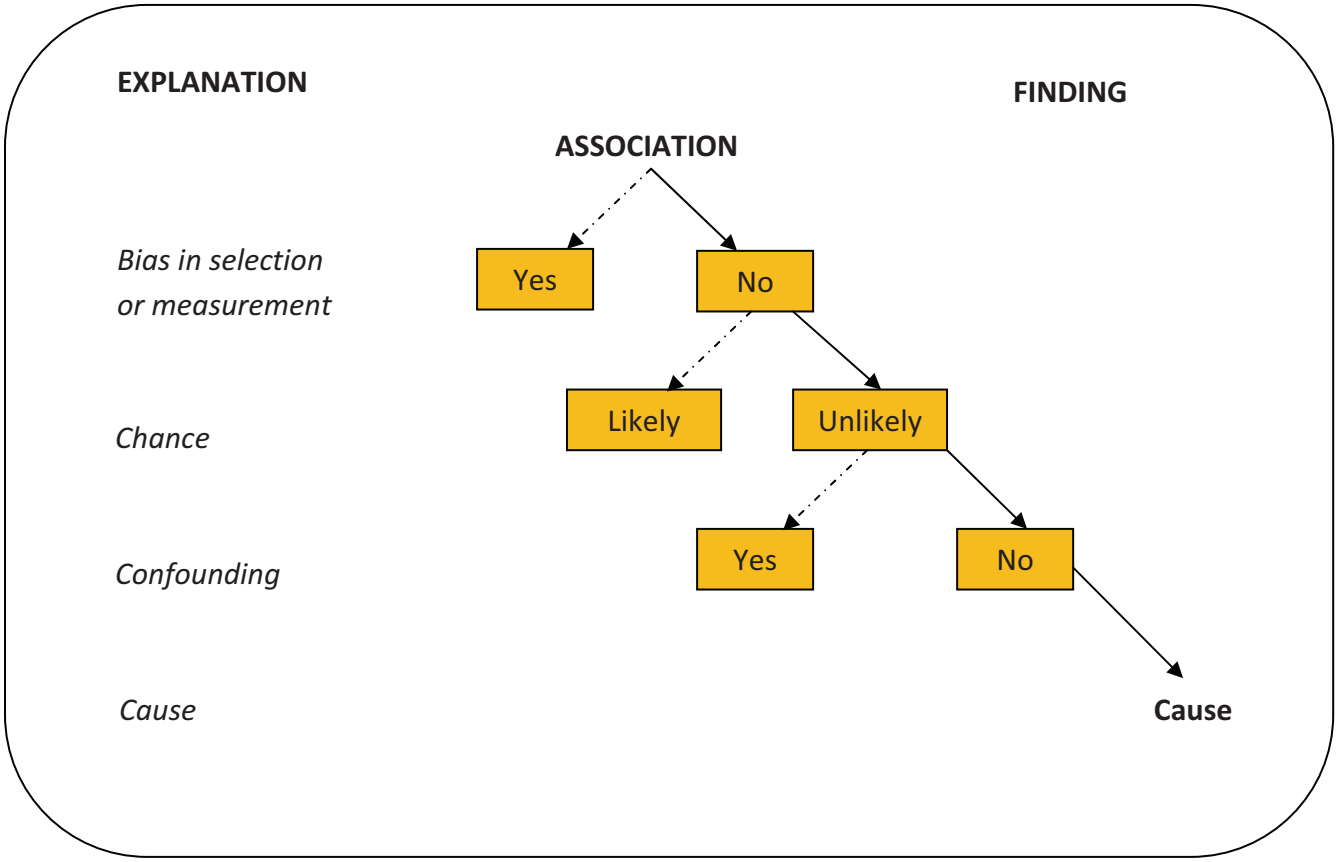
† Adjusted for patient characteristics (stroke severity, Charlson Index, diabetes mellitus, atrial fibrillation, myocardial infarction, hypertension, former stroke, intermittent claudication, percentage of fulfilled indicators, smoking, alcohol, type of residence and civil status)

5. Discussion

5.1 Strengths and limitations of the methodology

In assessing the validity of the findings from these four studies, it was necessary to consider whether the association might be an artifact from bias, confounding, or random variation. Figure 6 outlines these alternative explanations.

Figure 6. Association and cause. From *Clinical Epidemiology – The Essentials*.[85]



5.1.1 Selection bias

Selection bias occurs when the association between exposure and outcome is different for those included and those not included in the study.[107] This could seriously impede the external validity of the study. A selection bias also occurs when the loss of patients to follow-up is different among

those exposed and unexposed to the drug, which could impede internal validity. However, all studies in this thesis were based on nation-wide population-based registers with data of high validity that had nearly complete follow-up. Thus, the possibility of selection bias was limited. Patients for all the studies were obtained from the DNIP database, which requires the participation of all clinical units and departments in Denmark that treat patients with stroke. Also, regular, structured audits were conducted by DNIP on national, regional, and local scales. These audits included a validation of the agreement between patient registration and hospital discharge registries.

Although, in general, selection bias was likely to be a minor problem in studies I-IV, it should be noted that a systematic bias was probably introduced in study III, due to the study design. In that study, we analyzed continued drug use. Because the group studied was restricted to patients that survived at least 18 months after discharge, we thereby introduced an immortality bias. Our approach caused our estimates to be "best case scenarios"; i.e., we were likely to have overestimated the "real" proportion of patients with continued drug use. However, we chose this approach because alternative approaches could have introduced more unpredictable biases, due to the difficulties in making accurate estimates of prescription length based on registry data.

Another systematic error is the concept of *competing risk*. An essential disadvantage of using risk for assessing the occurrence of illness is that, over any extended time interval, it is usually technically impossible to measure risk because some people in the study population will die from causes other than the outcome under study.[107] Thus, those people were affected by a competing risk. For example, in study IV, we assessed the cumulative incidence of both AMI and recurrent stroke. However, not all patients survived for the entire follow-up period. Some patients died from causes other than AMI or recurrent stroke; e.g., infections, cancer, accidents etc. When the competing risk of death is not taken into account, the result will underestimate the risk of AMI or recurrent stroke in a patient population followed for five years. Therefore, we computed the cumulative incidences of AMI or recurrent stroke events over a period of five years, and took into account the competing risk of all-cause deaths.

5.1.2 Information bias

Information bias refers to a distortion in the estimated effect due to a measurement error or misclassification of subjects on one or more variables. An information bias from misclassification may occur in follow-up studies when there is unequal diagnostic surveillance among exposure groups. Misclassification can be either differential (the exposure category is misclassified differentially, according to outcome status, or vice versa) or non-differential (the exposure category is misclassified independently of outcome status, or vice versa). A differential misclassification can lead to either an over- or underestimation of the true association; in contrast, a non-differential misclassification will, in most situations, produce a bias towards the null.[107]

All the studies in this thesis were based on data recorded prospectively; thus, any misclassification would most likely be non-differential. In addition, the validity of the data recorded by DNIP was assessed systematically on a regular basis during the national and regional audits. Furthermore, any misclassification of data on care in DNIP was unlikely to depend on patient age and thus, if present, would lessen our ability to detect age-related differences in quality of care and result in conservative risk estimates. Finally, although it might be a cause for concern that the eligibility for the specific processes of care was determined by the staff, as health professionals could prioritize differently, we found no differences in the proportion of women and men considered eligible for the different measures of care.

In studies III and IV, the data on drug exposure and outcomes (death, AMI, and recurrent stroke) were prospectively collected from several different registries. Therefore, the information on drug exposure was collected independently of the outcomes; thus, any misclassification would most likely be non-differential. However in study III, we were not able to determine from our data whether patients who did not use secondary medical prophylaxis after discharge had not received a prescription or whether the patient had failed to fill the prescription at the pharmacy. Yet, this will not have any influence on our results, albeit it will have influence on the interpretation of the results.

Also, in studies III and IV, we did not know whether patients who filled their prescriptions were actually compliant with the treatment; however, it is likely that they had high compliance once they filled their prescriptions, because patients paid for part of the cost of the drugs.

5.1.3 Confounding

For a variable to be considered a confounder, it must be associated with the exposure and the outcome of interest, but it cannot be a factor in the prospective pathway between exposure and outcome, and its presence must be imbalanced between groups. In other words, it must be an independent risk factor. There are several methods to account for confounders in observational studies. We have used the methods of restriction, stratification, and adjustment in multivariate regression analyses.[85]

In the studies included in this thesis, data were available on a wide range of covariates. Thus, it was possible to account for a number of potential confounders, including stroke severity, comorbidity, socioeconomic factors, and lifestyle factors.

However, our studies carried an inherent risk of confounding by indication. This occurs in the analysis of an intervention, when whatever has made a physician or health professional initiate the intervention (the "indication"), is also linked to the outcome.[85] This can cause either an over- or underestimation of the effect of the intervention. However, in all of the studies, the risk of confounding by indication was reduced by means of restriction. In studies I and II, the analyses only included patients with no contraindications against the specific interventions of interest, as assessed by the physicians or other relevant health professionals who treated the patients. In studies III and IV, the analyses were further restricted to patients that showed no contraindications towards the specific prophylactic drugs of interest during their hospitalization. In study IV, an additional analysis of groups stratified by propensity score was included, in order to overcome the potential problem that patients with long expected survival times may have been more likely to receive prescriptions for secondary medical prophylaxis than those with short expected survival times.

5.1.4 Chance

The concept of chance, or random error, is closely related to precision, because the mean of a large number of unbiased observations tends to approximate the true value in the population, even though the individual samples may vary considerably.[85] Therefore, large studies are more precise and contain less random error in the estimation than small studies. However, random error can never be totally eliminated, so precision and chance should always be considered in

assessments of clinical observations. The precision in studies I-IV was reflected by the width of the 95% confidence intervals. In all our main analyses, the large study populations resulted in high statistical precision. However, the statistical precision of the associations in some of the subanalyses was lower, due to either fewer included observations or further stratification of the main study population. Therefore, some caution is required when interpreting the findings from these subanalyses as they were more sensitive to chance.

5.2 Comparison with existing literature

5.2.1 Study I

Our findings are consistent with those from most other studies that found that older patients received lower quality of care than younger patients during hospitalization.[42, 62, 63] Similar to the findings of both Bhalla et al and Di Carlo et al, we found that older patients were less likely than younger patients to be examined with brain imaging;[62, 63] moreover, like Bhalla et al, we found less intensive physio- and occupational- therapeutic efforts in older compared to younger patients.[63] Also, Lamassa et al at found that, for stroke patients with atrial fibrillation, increasing age was an independent determinant for not receiving anticoagulant treatment.[42] This is in accordance with our findings in patients with atrial fibrillation; we found that eligible older patients were less likely than eligible younger patients to receive anticoagulant therapy during hospitalization. Furthermore, like Simpson et al, we did not find that older patients were more likely to receive antiplatelet therapy than younger patients during hospitalization.[80] Finally, the 30 day mortality found in our study was consistent with the findings of Di Carlo et al.[62] However, our overall results are not in accordance with the recent American study by Fonarow et al that found no age-related differences in stroke care during hospitalization.[64] On the other hand this study found that it is only within recent years that age-related differences appear to have disappeared, and participation in the GWTG-Stroke program is not mandatory in contrast to the DNIP is, which to some extent could explain our different findings.

5.2.2 Study II

Several studies have investigated whether there were sex-related differences for in-hospital care.[44, 65-69, 71, 72, 74, 83] In our study, we found no substantial sex-related differences in care during hospitalization. This was in agreement with a number of studies, including a study and a meta-

analysis that were published after our study.[44, 65-68] Like our study, those studies showed no unequivocal evidence of sex-related differences in the use of neuroimaging, antithrombotic treatment, admission to specialized stroke units, occupational therapy, or physiotherapy. The remaining studies did find sex-related differences in early hospital admission, antithrombotic treatment, anticoagulant therapy, brain imaging, occupational therapy, or physiotherapy.[69, 71, 72, 74, 83] In our study, the lower mortality among women confirmed findings from other studies on patients with stroke, including a previous study based on data from the DNIP.[68, 84, 108] These studies supported the hypothesis that women may have a physiological advantage for surviving a stroke, because the survival rate of women remained higher than that of men after taking into account the differences in prognostic profile, lifestyle, and quality of early care.

5.2.3 Study III

A number of studies have investigated either age- or sex-related differences in the use of various secondary medical prophylaxes in patients with stroke[42, 44, 67, 73-75, 79, 80]; however the majority of those studies were based on in-hospital differences, rather than differences that occurred after hospital discharge. Our findings of age-related differences were in accordance with some of these studies. Our overall finding of an age-related decline in the continued use of secondary prophylactic drugs after discharge was supported by findings from a recent Swedish study.[75] We found that the use of oral anticoagulants was particularly low among older patients; this was in accordance with findings from Lamassa et al, who found that increasing age was a determinant for not receiving anticoagulant treatment three months after stroke, and with a Swedish study that found that advanced age was associated with low persistence in warfarin treatment.[42, 75] In addition, in study I, we found that the low use of anticoagulant therapy observed among older patients during hospitalization was followed by a similarly low use of oral anticoagulant therapy among older patients after hospital discharge. Furthermore, the low use of statins among older patients was in accordance with findings from the Austrian study by Lalouschek et al, who also found that older patients were less likely to receive statin therapy after hospital discharge.[79]

Our findings regarding sex-related differences in secondary medical prophylaxis were in agreement with those of Simpson et al, who found that women were more likely than men to receive a prescription for thiazide diuretics.[80] Our overall findings regarding in the initiation of medical prophylaxis during the first six months after discharge were in agreement with the recent

study by Eriksson et al, who found no sex-related differences in antihypertensive, antithrombotic, and anticoagulant therapies prescribed at hospital discharge.[67] Unlike Eriksson et al, we found that women were less likely than men to receive prophylactic antihypertensive treatment in the form of ACE inhibitors/ATII antagonists. However, the study by Eriksson et al did not distinguish between different types of antihypertensive treatments. Also, we did not find that women were less likely than men to receive lipid lowering drugs following discharge.

Our results did not agree with other sex-related differences found in the Eriksson et al study or any of the other studies. Those studies found sex-related differences in the overall use of antithrombotic, anticoagulant, antihypertensive, and statin therapies.[44, 73, 74, 80]

5.2.4 Study IV

In our study, the use of a wide range of cardiovascular drugs in secondary stroke prophylaxis was associated with a lower mortality. This finding was in accordance with the few existing studies, that examined this issue.[86, 88] Those studies also found that antiplatelet and antihypertensive therapies were associated with a lower risk of death in patients with ischemic stroke. Another study found that antiplatelet and statin therapies were effective for reducing the risk of cerebrovascular events and other vascular events.[87, 99] In contrast, we found that statin therapy was effective in reducing the risk of AMI and recurrent stroke events, but we could not confirm an association for antiplatelet therapy. The remaining literature investigated the effectiveness of primary prophylactic treatment in preventing stroke and reducing its severity.[89-97] All studies that examined oral anticoagulant therapy found that it was effective for preventing ischemic stroke in patients with atrial fibrillation.[89-96] This was in accordance with our findings on the effectiveness of secondary prophylactic oral anticoagulant therapy in patients with ischemic stroke and atrial fibrillation. Our findings that oral anticoagulant therapy appeared to be more effective among women than men with atrial fibrillation for reducing the rate of recurrent stroke was supported by the results on anticoagulant/antithrombotic efficacy in the study by Fang et al and by an analysis of data pooled from five randomized trials.[82, 109] However, the apparent increased effectiveness of anticoagulant therapy for preventing stroke in women compared to men is most likely due to a combination of its increased effectiveness with increasing age and the fact that a larger proportion of women were in the group of older patients with stroke. On a similar note, Frost et al found that oral anticoagulant therapy was most effective in preventing stroke among younger compared to

older male patients.[91] That result was opposite to the findings by Fang et al, but the latter results were also likely to be explained by a larger proportion of males in the group of younger patients compared to the group of older patients with stroke.

Regarding antihypertensive therapy, Klungel et al found that thiazide diuretics were associated with a lower risk of recurrent stroke, and other antihypertensive drugs were associated with a higher risk of recurrent stroke.[97] Our results did not confirm this pattern in relation to recurrent stroke; instead, we found a similar pattern for AMI following stroke where use of antihypertensives other than thiazide diuretics was associated with an increased risk of AMI. With regard to recurrent stroke, we found that beta blocker therapy and thiazide diuretic therapy was associated with an increased risk of recurrent stroke.

6. Conclusions

6.1 Study I:

- In Denmark, older patients with stroke received lower quality acute in-hospital stroke care than younger patients with stroke; this was most significant for early oral anticoagulant therapy and early assessment of nutritional risk.
- The age-related differences in quality of care did not appear to explain the higher mortality among older patients.

6.2 Study II:

- There appeared to be no substantial sex-related differences in acute in-hospital stroke care in Denmark.
- Therefore, sex-related differences in short term mortality were most likely explained by other factors.

6.3 Study III:

- Older patients with ischemic stroke were less likely than younger patients to both receive and continue the use of secondary medical prophylaxis following hospital discharge.

- The reduced use of secondary medical prophylaxis contributed to the increased mortality rate ratios in older patients compared to younger patients.

6.4 Study IV:

- Overall, secondary medical prophylactic treatment was associated with a lower risk of all-cause death, and to some extent, lower risks of AMI and recurrent stroke.

- For some drugs, effectiveness varied depending on age of the patients but not on sex; this was most pronounced for antiplatelet therapy, where effectiveness decreased with increasing age, and for oral anticoagulant therapy, where effectiveness increased with increasing age.

7. Perspectives

Cerebrovascular events are often a serious manifestation of systemic vascular disease. Nevertheless, they have, for various reasons, historically received less attention in the health care system than coronary vascular diseases. However, in 2005, Peter Rothwell and colleagues published a report from the Oxford Vascular Study, in which they determined the incidence and short-term outcomes of three acute manifestations of atherosclerosis: coronary, cerebral, and peripheral events. This study challenged some of the prevailing dogma and contradicted previous hypotheses, because the results suggested that acute cerebrovascular events were as common, or more common, than acute coronary events (overall relative incidence 1.19, 95%CI: 1.06-1.33).[110] Furthermore, Rothwell and colleagues showed that the event and incidence rates rose steeply with increasing age in all arterial regions.

In a report from the Danish MONICA study published in 1999, Thorvaldsen and colleagues showed that, despite medical advancements that have reduced age-adjusted stroke incidence rates, the improvements were nearly entirely counterbalanced by an aging population.[111] This should be considered alongside the fact that the proportion of older individuals in the Western world is increasing. In Denmark, the proportion of citizens over 65 years of age is expected to increase by 76% by 2042. This will result in 1.54 million citizens over the age of 65, compared to the current

875 500 citizens over the age of 65.[112] Thus, the age-specific incidence of stroke must be considerably reduced in order to counteract the demographic changes in the population.

This thesis demonstrated that older patients with stroke received less intensive medical care than younger patients with stroke; this was true both for care during hospitalization and for secondary medical prophylactic treatment after hospital discharge. Moreover, we have demonstrated that older patients with stroke did not receive some of the most effective secondary medical prophylactic drugs. Fortunately, we did not find any significant sex-related differences in care or use of secondary medical prophylaxis. Consistent with many other studies, our findings showed that female patients experienced stroke at a higher mean age and with higher severity than male patients. Therefore, it is very likely that the majority of sex-related differences found in previous publications might be largely explained by the age differences among male and female patients with stroke.

We were not able to evaluate the effects of age-related differential treatment on other relevant endpoints; e.g., functional capacity after discharge or quality of life; however, it is very likely that insufficient treatment and care among older patients will also have a significantly negative association with those endpoints. Therefore, further investigation is required to determine whether age-related differential treatment during hospitalization has consequences on other important or more sensitive clinical outcomes.

This thesis, combined with the known data on stroke incidence and demographic changes in the population, underlines an important need to optimize acute treatment and both primary and secondary prophylaxis for stroke, regardless of patient age. This study uncovered the extent and nature of any age- or sex-related differences in diagnostics, treatment, care, and prevention as a precondition to ensure that evidence-based practice is offered to all stroke patients. However, this information alone is not sufficient to change practice. Our findings need to be followed up by qualitative studies to advance the understanding of the mechanisms behind this problem and by developing interventions of education, information and auditing. These steps towards eliminating age-differential treatment in stroke care should be implemented as soon as possible to ameliorate the current dramatic increases in the economic and societal burden of stroke.

8. Summary

Among the health care issues that are currently under intense debate, are the extent and implications of possible age- and sex-related differences in acute and secondary prophylactic treatment and care following stroke. Several studies suggested that differential care was given according to the age and sex of patients with stroke, and that these differences may have had severe clinical consequences for the patients. Furthermore, only sparse data exist on the effectiveness of secondary medical prophylaxis following ischemic stroke. In order to further examine this topic, we conducted four studies; the first two studies aimed to determine whether there were age- and sex-related differences in acute stroke care in Denmark and if so, whether these differences contributed to age- and sex-related differences in mortality following stroke. The last two studies explored potential age- and sex-related differences in the use of secondary medical prophylaxis following stroke, and drug effectiveness in reducing mortality and the risks of myocardial infarction and recurrent stroke. All studies were based on data from the Danish National Indicator Project (DNIP), which is a nationwide initiative to monitor and improve the quality of care for specific diseases, including stroke. The DNIP develops and implements evidence-based quality of care indicators. DNIP database was linked with the National Registry of Patients, the Medicines Agency Denmark, the Danish Civil Registration System, and the Integrated Database for Labour Market Research in order to obtain patient-specific data on hospital discharges, vital status, filled prescriptions, and socioeconomic status. The first two studies included approximately 30 000 patients admitted with stroke from 2003 to 2005; the last two studies included approximately 29 000 patients with ischemic stroke from 2003 to 2006. The studies were designed as nationwide, population-based, follow-up studies. Data were analyzed with logistic regression and Cox proportional hazards regression. The first study showed that older stroke patients (>80 years) received lower quality acute care than younger patients (≤65 years); however the differences did not appear to explain the higher mortality among older patients. The second study found that, after stratification for age, there did not appear to be any substantial sex-related differences in acute hospital care. Therefore, the lower short-term mortality of females compared to males was most likely due to other factors. The third study showed that older patients (>80 years) were substantially less likely to receive secondary medical prophylaxis after hospital discharge following an ischemic stroke compared to younger patients (≤65 years). Older patients

were also less likely than younger patients to continue prophylactic drug use. The differences in use of secondary prophylaxis contributed to the higher mortality observed among older patients compared to younger patients. The last study (IV) found that secondary medical prophylaxis showed good overall effectiveness in relation to mortality and, to some extent, in relation to myocardial infarction and recurrent stroke events in patients with ischemic stroke following hospital discharge. For some drugs, the effectiveness varied with age. Thus, this factor should be taken into account when preparing a medical prophylactic regimen for an individual patient.

9. Dansk Resume

Omfanget og implikationerne af mulige alders- og kønsrelaterede forskelle i akut og sekundær profylaktisk behandling og pleje efter apopleksi er et omdiskuteret emne. Flere studier antyder, at patienter med apopleksi måske modtager forskelsbehandling på baggrund af alder og køn, og at disse forskelle kan have alvorlige kliniske konsekvenser for patienterne. Derudover eksisterer der kun sparsomme data vedrørende effektiviteten af sekundær medicinsk profylakse efter iskæmisk apopleksi. For yderligere at undersøge dette emne, blev der foretaget fire studier. Målet med de første to studier var at klarlægge, om der er alders- og kønsrelaterede forskelle i den akutte apopleksibehandling i Danmark, og i så fald, om disse forskelle eventuelt bidrager til alders- og kønsrelaterede forskelle i dødeligheden efter apopleksi. De to sidste studier var beregnet på at undersøge potentielle alders- og kønsrelaterede forskelle i brugen af sekundær medicinsk profylakse efter iskæmisk apopleksi samt effektiviteten af medikamenterne i forhold til dødelighed, risikoen for akut myocardie infarkt og tilbagevendende apopleksi. Alle studierne var baserede på data fra Det Nationale Indikatorprojekt (NIP), som er et nationalt initiativ til at monitorere og forbedre kvaliteten af behandling blandt udvalgte sygdomme, inklusiv apopleksi. Projektet gør dette ved at udvikle og implementere evidensbaserede indikatorer for behandlingskvalitet. NIP-registret blev sammenkoblet med Landspatientregistret, Lægemiddelstyrrelsens lægemiddelstatistikregister og CPR-registret samt den Integrerede Database for Arbejdsmarkedsforskning for at indhente informationer vedrørende patienters udskrivningsdata, vitale status, indløste recepter og socioøkonomiske status. De første to studier inkluderede ca. 30 000 patienter indlagt med apopleksi fra 2003 til 2005, mens de to sidste studier inkluderede ca. 29 000 patienter indlagt med iskæmisk apopleksi fra 2003 til 2006. Studierne blev

designet som landsdækkende populationsbaserede follow-up studier. Data blev analyseret ved brug af logistisk regression og Cox proportional hazards regression. Det første studie viste, at ældre patienter (>80 år) modtog en ringere kvalitet af behandling og pleje end yngre patienter (≤65 år), dog lod forskellene ikke til at kunne forklare den højere dødelighed blandt ældre patienter. Det andet studie fandt, at der ikke lod til at være nogle væsentlige kønsrelaterede forskelle i den akutte hospitalsbehandling efter stratificering, og at den lavere kort-tids dødelighed hos kvinder derfor sandsynligvist skal forklares af andre faktorer. Det tredje studie viste, at ældre patienter (>80 år) havde en langt mindre sandsynlighed for at modtage sekundær medicinsk profylakse efter en iskæmisk apopleksi sammenlignet med yngre patienter (≤65 år). Ældre patienter, som påbegyndte brug af sekundær profylakse, havde også en mindre sandsynlighed for at fortsætte behandlingen, og forskellene i brugen af sekundær medicinsk profylakse bidrog til den højere dødelighed, som kunne observeres blandt ældre patienter. Det fjerde og sidste studie fandt, at den overordnede effektivitet af sekundær medicinsk profylakse i forhold til dødelighed, og i nogen grad i forhold til myocardie infarkt og tilbagevendende apopleksi, efter udskrivelse var god. For nogle medikamenter varierede effektiviteten alt efter alder, hvilket tyder på, at denne faktor bør tages i betragtning, når en medicinsk profylaktisk behandlingsplan udvikles for den enkelte patient.

Reference List

(1) International Cardiovascular Disease Statistics. 2007.
Ref Type: Generic

(2) WHO. World Health Report. 2002.
Ref Type: Generic

(3) Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. *Lancet Neurol* 2009 April;8(4):355-69.

(4) Hjernesagen internetlink. www.hjernesagen.dk. 2006.
Ref Type: Generic

(5) Referenceprogram for Behandling af Patienter med Apopleksi.
www.sst.dk/publ/Publ2006/CEMTV/SfR/Apopl_refprg.pdf . 2006.
Ref Type: Generic

(6) Appelros P, Stegmayr B, Terent A. Sex differences in stroke epidemiology: a systematic review. *Stroke* 2009 April;40(4):1082-90.

(7) The World Health Organization MONICA Project (monitoring trends and determinants in cardiovascular disease): a major international collaboration. WHO MONICA Project Principal Investigators. *J Clin Epidemiol* 1988;41(2):105-14.

(8) Warlow C. *Stroke*
a practical guide to management. 2nd ed ed. Oxford: Blackwell Science; 2001.

(9) Elkind MS, Sacco RL. Stroke risk factors and stroke prevention. *Semin Neurol* 1998;18(4):429-40.

(10) Allen CL, Bayraktutan U. Risk factors for ischaemic stroke. *Int J Stroke* 2008 May;3(2):105-16.

(11) MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, Abbott R, Godwin J, Dyer A, Stamler J. Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990 March 31;335(8692):765-74.

(12) Bornstein NM, Aronovich BD, Karepov VG, Gur AY, Treves TA, Oved M, Korczyn AD. The Tel Aviv Stroke Registry. 3600 consecutive patients. *Stroke* 1996 October;27(10):1770-3.

(13) Moulin T, Tatu L, Crepin-Leblond T, Chavot D, Berges S, Rumbach T. The Besancon Stroke Registry: an acute stroke registry of 2,500 consecutive patients. *Eur Neurol* 1997;38(1):10-20.

(14) Warlow CP. Epidemiology of stroke. *Lancet* 1998 October;352 Suppl 3:SIII1-SIII4.

(15) Referenceprogram for Behandling af Patienter med Apopleksi. 2009.
Ref Type: Generic

(16) Organised inpatient (stroke unit) care for stroke. *Cochrane Database Syst Rev* 2007;(4):CD000197.

(17) Ingeman A, Pedersen L, Hundborg HH, Petersen P, Zielke S, Mainz J, Bartels P, Johnsen SP. Quality of care and mortality among patients with stroke: a nationwide follow-up study. *Med Care* 2008 January;46(1):63-9.

(18) Candelise L, Gattinoni M, Bersano A, Micieli G, Sterzi R, Morabito A. Stroke-unit care for acute stroke patients: an observational follow-up study. *Lancet* 2007 January 27;369(9558):299-305.

(19) Adams HP, Jr., del ZG, Alberts MJ, Bhatt DL, Brass L, Furlan A, Grubb RL, Higashida RT, Jauch EC, Kidwell C, Lyden PD, Morgenstern LB, Qureshi AI, Rosenwasser RH, Scott PA, Wijdicks EF. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Stroke* 2007 May;38(5):1655-711.

(20) Wardlaw JM, Murray V, Berge E, Del Zoppo GJ. Thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev* 2009;(4):CD000213.

(21) Wahlgren N, Ahmed N, Eriksson N, Aichner F, Bluhmki E, Davalos A, Erila T, Ford GA, Grond M, Hacke W, Hennerici MG, Kaste M, Kohrmann M, Larrue V, Lees KR, Machnig T, Roine RO, Toni D, Vanhooren G. Multivariable analysis of outcome predictors and adjustment of main outcome results to baseline data profile in randomized controlled trials: Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy (SITS-MOST). *Stroke* 2008 December;39(12):3316-22.

(22) Wahlgren N, Ahmed N, Davalos A, Hacke W, Millan M, Muir K, Roine RO, Toni D, Lees KR. Thrombolysis with alteplase 3-4.5 h after acute ischaemic stroke (SITS-ISTR): an observational study. *Lancet* 2008 October 11;372(9646):1303-9.

(23) Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, Larrue V, Lees KR, Medeghri Z, Machnig T, Schneider D, von KR, Wahlgren N, Toni D. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008 September 25;359(13):1317-29.

(24) Poor nutritional status on admission predicts poor outcomes after stroke: observational data from the FOOD trial. *Stroke* 2003 June;34(6):1450-6.

(25) Svendsen ML, Ehlers LH, Andersen G, Johnsen SP. Quality of care and length of hospital stay among patients with stroke. *Med Care* 2009 May;47(5):575-82.

(26) Bernhardt J, Dewey H, Thrift A, Collier J, Donnan G. A very early rehabilitation trial for stroke (AVERT): phase II safety and feasibility. *Stroke* 2008 February;39(2):390-6.

(27) Horn SD, DeJong G, Smout RJ, Gassaway J, James R, Conroy B. Stroke rehabilitation patients, practice, and outcomes: is earlier and more aggressive therapy better? *Arch Phys Med Rehabil* 2005 December;86(12 Suppl 2):S101-S114.

(28) Legg L, Drummond A, Leonardi-Bee J, Gladman JR, Corr S, Donkervoort M, Edmans J, Gilbertson L, Jongbloed L, Logan P, Sackley C, Walker M, Langhorne P. Occupational therapy for patients with

problems in personal activities of daily living after stroke: systematic review of randomised trials. *BMJ* 2007 November 3;335(7626):922.

(29) Chen ZM, Sandercock P, Pan HC, Counsell C, Collins R, Liu LS, Xie JX, Warlow C, Peto R. Indications for early aspirin use in acute ischemic stroke : A combined analysis of 40 000 randomized patients from the chinese acute stroke trial and the international stroke trial. On behalf of the CAST and IST collaborative groups. *Stroke* 2000 June;31(6):1240-9.

(30) Gubitz G, Sandercock P, Counsell C. Antiplatelet therapy for acute ischaemic stroke. *Cochrane Database Syst Rev* 2000;(2):CD000029.

(31) Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002 January 12;324(7329):71-86.

(32) Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci* 1996 November;143(1-2):1-13.

(33) Halkes PH, van GJ, Kappelle LJ, Koudstaal PJ, Algra A. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. *Lancet* 2006 May 20;367(9523):1665-73.

(34) De Schryver EL, Algra A, van GJ. Dipyridamole for preventing stroke and other vascular events in patients with vascular disease. *Cochrane Database Syst Rev* 2007;(3):CD001820.

(35) A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet* 1996 November 16;348(9038):1329-39.

(36) Sacco RL, Diener HC, Yusuf S, Cotton D, Ounpuu S, Lawton WA, Palesch Y, Martin RH, Albers GW, Bath P, Bornstein N, Chan BP, Chen ST, Cunha L, Dahlof B, De KJ, Donnan GA, Estol C, Gorelick P, Gu V, Hermansson K, Hilbrich L, Kaste M, Lu C, Machnig T, Pais P, Roberts R, Skvortsova V, Teal P, Toni D, VanderMaelen C, Voigt T, Weber M, Yoon BW. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *N Engl J Med* 2008 September 18;359(12):1238-51.

(37) Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, Flather MD, Haffner SM, Hamm CW, Hankey GJ, Johnston SC, Mak KH, Mas JL, Montalescot G, Pearson TA, Steg PG, Steinhubl SR, Weber MA, Brennan DM, Fabry-Ribaudo L, Booth J, Topol EJ. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006 April 20;354(16):1706-17.

(38) Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) Study Group. *Lancet* 1993 November 20;342(8882):1255-62.

(39) Saxena R, Koudstaal PJ. Anticoagulants for preventing stroke in patients with nonrheumatic atrial fibrillation and a history of stroke or transient ischaemic attack. *Cochrane Database Syst Rev* 2004;(2):CD000185.

(40) Hart RG, Pearce LA, Koudstaal PJ. Transient ischemic attacks in patients with atrial fibrillation: implications for secondary prevention: the European Atrial Fibrillation Trial and Stroke Prevention in Atrial Fibrillation III trial. *Stroke* 2004 April;35(4):948-51.

(41) Gladstone DJ, Bui E, Fang J, Laupacis A, Lindsay MP, Tu JV, Silver FL, Kapral MK. Potentially preventable strokes in high-risk patients with atrial fibrillation who are not adequately anticoagulated. *Stroke* 2009 January;40(1):235-40.

(42) Lamassa M, Di CA, Pracucci G, Basile AM, Trefoloni G, Vanni P, Spolveri S, Baruffi MC, Landini G, Ghetti A, Wolfe CD, Inzitari D. Characteristics, outcome, and care of stroke associated with atrial fibrillation in Europe: data from a multicenter multinational hospital-based registry (The European Community Stroke Project). *Stroke* 2001 February;32(2):392-8.

(43) Reeves M, Bhatt A, Jajou P, Brown M, Lisabeth L. Sex differences in the use of intravenous rt-PA thrombolysis treatment for acute ischemic stroke: a meta-analysis. *Stroke* 2009 May;40(5):1743-9.

(44) Smith DB, Murphy P, Santos P, Phillips M, Wilde M. Gender differences in the Colorado Stroke Registry. *Stroke* 2009 April;40(4):1078-81.

(45) Humphries KH, Jackevicius C, Gong Y, Svensen L, Cox J, Tu JV, Laupacis A. Population rates of hospitalization for atrial fibrillation/flutter in Canada. *Can J Cardiol* 2004 July;20(9):869-76.

(46) Neal B, MacMahon S, Chapman N. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. Blood Pressure Lowering Treatment Trialists' Collaboration. *Lancet* 2000 December 9;356(9246):1955-64.

(47) Hildebrandt PR, Tuxen CD, Kjeldsen SE, Lund-Johansen P, Hansson L. [Are newer antihypertensive agents better than the older ones? Results of trials (CAPPP, STOP-2, NORDIL, INSIGHT and ALLHAT) with newer antihypertensive agents]. *Ugeskr Laeger* 2001 December 31;164(1):18-21.

(48) Wang JG, Li Y, Franklin SS, Safar M. Prevention of stroke and myocardial infarction by amlodipine and Angiotensin receptor blockers: a quantitative overview. *Hypertension* 2007 July;50(1):181-8.

(49) Post-stroke antihypertensive treatment study. A preliminary result. PATS Collaborating Group. *Chin Med J (Engl)* 1995 September;108(9):710-7.

(50) Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000 January 20;342(3):145-53.

(51) Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001 September 29;358(9287):1033-41.

(52) Fransen M, Anderson C, Chalmers J, Chapman N, Davis S, MacMahon S, Neal B, Sega R, Terent A, Tzourio C, Woodward M. Effects of a perindopril-based blood pressure-lowering regimen on disability and dependency in 6105 patients with cerebrovascular disease: a randomized controlled trial. *Stroke* 2003 October;34(10):2333-8.

(53) Tzourio C, Anderson C, Chapman N, Woodward M, Neal B, MacMahon S, Chalmers J. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. *Arch Intern Med* 2003 May 12;163(9):1069-75.

(54) Diener HC, Sacco RL, Yusuf S, Cotton D, Ounpuu S, Lawton WA, Palesch Y, Martin RH, Albers GW, Bath P, Bornstein N, Chan BP, Chen ST, Cunha L, Dahlof B, De KJ, Donnan GA, Estol C, Gorelick P, Gu V, Hermansson K, Hilbrich L, Kaste M, Lu C, Machnig T, Pais P, Roberts R, Skvortsova V, Teal P, Toni D, VanderMaelen C, Voigt T, Weber M, Yoon BW. Effects of aspirin plus extended-release dipyridamole versus clopidogrel and telmisartan on disability and cognitive function after recurrent stroke in patients with ischaemic stroke in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial: a double-blind, active and placebo-controlled study. *Lancet Neurol* 2008 October;7(10):875-84.

(55) Amarenco P, Bogousslavsky J, Callahan A, III, Goldstein LB, Hennerici M, Rudolph AE, Sillesen H, Simunovic L, Szarek M, Welch KM, Zivin JA. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med* 2006 August 10;355(6):549-59.

(56) MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002 July 6;360(9326):7-22.

(57) Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet* 1998 May 9;351(9113):1379-87.

(58) Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med* 1991 August 15;325(7):445-53.

(59) American Heart Association. American Stroke Association. Heart Disease and Stroke Statistics 2008 Update. 2008.

(60) Stevens A. *Health care needs assessment*
***the epidemiologically based needs assessment reviews*. 2nd ed ed. Oxford: Radcliffe; 2004.**

(61) Kwakkel G, Wagenaar RC, Kollen BJ, Lankhorst GJ. Predicting disability in stroke--a critical review of the literature. *Age Ageing* 1996 November;25(6):479-89.

(62) Di CA, Lamassa M, Pracucci G, Basile AM, Trefoloni G, Vanni P, Wolfe CD, Tilling K, Ebrahim S, Inzitari D. Stroke in the very old : clinical presentation and determinants of 3-month functional outcome: A European perspective. European BIOMED Study of Stroke Care Group. *Stroke* 1999 November;30(11):2313-9.

(63) Bhalla A, Grieve R, Tilling K, Rudd AG, Wolfe CD. Older stroke patients in Europe: stroke care and determinants of outcome. *Age Ageing* 2004 November;33(6):618-24.

(64) Fonarow GC, Reeves MJ, Zhao X, Olson DM, Smith EE, Saver JL, Schwamm LH. Age-related differences in characteristics, performance measures, treatment trends, and outcomes in patients with ischemic stroke. *Circulation* 2010 February 23;121(7):879-91.

(65) Kapral MK, Fang J, Hill MD, Silver F, Richards J, Jaigobin C, Cheung AM. Sex differences in stroke care and outcomes: results from the Registry of the Canadian Stroke Network. *Stroke* 2005 April;36(4):809-14.

(66) Muller-Nordhorn J, Nolte CH, Rossnagel K, Jungehulsing GJ, Reich A, Roll S, Villringer A, Willich SN. Medical management in patients following stroke and transitory ischemic attack: a comparison between men and women. *Cerebrovasc Dis* 2006;21(5-6):329-35.

(67) Eriksson M, Glader EL, Norrving B, Terent A, Stegmayr B. Sex differences in stroke care and outcome in the Swedish national quality register for stroke care. *Stroke* 2009 March;40(3):909-14.

(68) Appelros P, Stegmayr B, Terent A. A review on sex differences in stroke treatment and outcome. *Acta Neurol Scand* 2009 November 30.

(69) Foerch C, Misselwitz B, Humpich M, Steinmetz H, Neumann-Haefelin T, Sitzer M. Sex disparity in the access of elderly patients to acute stroke care. *Stroke* 2007 July;38(7):2123-6.

(70) Gargano JW, Wehner S, Reeves MJ. Do presenting symptoms explain sex differences in emergency department delays among patients with acute stroke? *Stroke* 2009 April;40(4):1114-20.

(71) Di CA, Lamassa M, Baldereschi M, Pracucci G, Basile AM, Wolfe CD, Giroud M, Rudd A, Ghetti A, Inzitari D. Sex differences in the clinical presentation, resource use, and 3-month outcome of acute stroke in Europe: data from a multicenter multinational hospital-based registry. *Stroke* 2003 May;34(5):1114-9.

(72) Gargano JW, Wehner S, Reeves M. Sex differences in acute stroke care in a statewide stroke registry. *Stroke* 2008 January;39(1):24-9.

(73) Reeves MJ, Fonarow GC, Zhao X, Smith EE, Schwamm LH. Quality of care in women with ischemic stroke in the GWTG program. *Stroke* 2009 April;40(4):1127-33.

(74) Holroyd-Leduc JM, Kapral MK, Austin PC, Tu JV. Sex differences and similarities in the management and outcome of stroke patients. *Stroke* 2000 August;31(8):1833-7.

(75) Glader EL, Sjolander M, Eriksson M, Lundberg M. Persistent use of secondary preventive drugs declines rapidly during the first 2 years after stroke. *Stroke* 2010 February;41(2):397-401.

(76) van WC, Hart RG, Connolly S, Austin PC, Mant J, Hobbs FD, Koudstaal PJ, Petersen P, Perez-Gomez F, Knottnerus JA, Boode B, Ezekowitz MD, Singer DE. Effect of age on stroke prevention therapy in patients with atrial fibrillation: the atrial fibrillation investigators. *Stroke* 2009 April;40(4):1410-6.

(77) Fang MC, Go AS, Hylek EM, Chang Y, Henault LE, Jensvold NG, Singer DE. Age and the risk of warfarin-associated hemorrhage: the anticoagulation and risk factors in atrial fibrillation study. *J Am Geriatr Soc* 2006 August;54(8):1231-6.

(78) Ovbiagele B, Saver JL, Bang H, Chambless LE, Nassief A, Minuk J, Toole JF, Crouse JR. Statin treatment and adherence to national cholesterol guidelines after ischemic stroke. *Neurology* 2006 April 25;66(8):1164-70.

(79) Lalouschek W, Lang W, Greisenegger S, Mullner M. Determination of lipid profiles and use of statins in patients with ischemic stroke or transient ischemic attack. *Stroke* 2003 January;34(1):105-10.

(80) Simpson CR, Wilson C, Hannaford PC, Williams D. Evidence for age and sex differences in the secondary prevention of stroke in Scottish primary care. *Stroke* 2005 August;36(8):1771-5.

(81) Fairhead JF, Rothwell PM. Underinvestigation and undertreatment of carotid disease in elderly patients with transient ischaemic attack and stroke: comparative population based study. *BMJ* 2006 September 9;333(7567):525-7.

(82) Fang MC, Singer DE, Chang Y, Hylek EM, Henault LE, Jensvold NG, Go AS. Gender differences in the risk of ischemic stroke and peripheral embolism in atrial fibrillation: the AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) study. *Circulation* 2005 September 20;112(12):1687-91.

(83) Glader EL, Stegmayr B, Norrving B, Terent A, Hulter-Asberg K, Wester PO, Asplund K. Sex differences in management and outcome after stroke: a Swedish national perspective. *Stroke* 2003 August;34(8):1970-5.

(84) Olsen TS, Dehlendorff C, Andersen KK. Sex-related time-dependent variations in post-stroke survival--evidence of a female stroke survival advantage. *Neuroepidemiology* 2007;29(3-4):218-25.

(85) Fletcher RH, Wagner EH. *Clinical epidemiology the essentials*. 3rd ed ed. Baltimore: Williams & Wilkins; 1996.

(86) Ding D, Lu CZ, Fu JH, Hong Z. Association of antiplatelet therapy with lower risk of death and recurrent cerebrovascular events after ischemic stroke--results from the China Ischemic Stroke Registry Study. *Circ J* 2009 December;73(12):2342-7.

(87) Ding D, Lu CZ, Fu JH, Hong Z. Predictors of vascular events after ischemic stroke: the china ischemic stroke registry study. *Neuroepidemiology* 2010;34(2):110-6.

(88) Kong FY, Tao WD, Hao ZL, Liu M. Predictors of one-year disability and death in Chinese hospitalized women after ischemic stroke. *Cerebrovasc Dis* 2010 February;29(3):255-62.

(89) Caro JJ, Flegel KM, Orejuela ME, Kelley HE, Speckman JL, Migliaccio-Walle K. Anticoagulant prophylaxis against stroke in atrial fibrillation: effectiveness in actual practice. *CMAJ* 1999 September 7;161(5):493-7.

(90) Aronow WS, Ahn C, Kronzon I, Gutstein H. Incidence of new thromboembolic stroke in persons 62 years and older with chronic atrial fibrillation treated with warfarin versus aspirin. *J Am Geriatr Soc* 1999 March;47(3):366-8.

(91) Frost L, Johnsen SP, Pedersen L, Toft E, Husted S, Sorensen HT. Atrial fibrillation or flutter and stroke: a Danish population-based study of the effectiveness of oral anticoagulation in clinical practice. *J Intern Med* 2002 July;252(1):64-9.

(92) Go AS, Hylek EM, Chang Y, Phillips KA, Henault LE, Capra AM, Jensvold NG, Selby JV, Singer DE. Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? *JAMA* 2003 November 26;290(20):2685-92.

(93) Darkow T, Vanderplas AM, Lew KH, Kim J, Hauch O. Treatment patterns and real-world effectiveness of warfarin in nonvalvular atrial fibrillation within a managed care system. *Curr Med Res Opin* 2005 October;21(10):1583-94.

(94) **Birman-Deych E, Radford MJ, Nilasena DS, Gage BF. Use and effectiveness of warfarin in Medicare beneficiaries with atrial fibrillation. *Stroke* 2006 April;37(4):1070-4.**

(95) **Lakshminarayan K, Solid CA, Collins AJ, Anderson DC, Herzog CA. Atrial fibrillation and stroke in the general medicare population: a 10-year perspective (1992 to 2002). *Stroke* 2006 August;37(8):1969-74.**

(96) **Parkash R, Wee V, Gardner MJ, Cox JL, Thompson K, Brownell B, Anderson DR. The impact of warfarin use on clinical outcomes in atrial fibrillation: a population-based study. *Can J Cardiol* 2007 May 1;23(6):457-61.**

(97) **Klungel OH, Heckbert SR, Longstreth WT, Jr., Furberg CD, Kaplan RC, Smith NL, Lemaitre RN, Leufkens HG, de BA, Psaty BM. Antihypertensive drug therapies and the risk of ischemic stroke. *Arch Intern Med* 2001 January 8;161(1):37-43.**

(98) **Yu AY, Keezer MR, Zhu B, Wolfson C, Cote R. Pre-stroke use of antihypertensives, antiplatelets, or statins and early ischemic stroke outcomes. *Cerebrovasc Dis* 2009;27(4):398-402.**

(99) **Lingsma HF, Steyerberg EW, Scholte Op Reimer WJ, van DR, Dippel DW. Statin treatment after a recent TIA or stroke: is effectiveness shown in randomized clinical trials also observed in everyday clinical practice? *Acta Neurol Scand* 2009 December 28.**

(100) **Mainz J, Krog BR, Bjornshave B, Bartels P. Nationwide continuous quality improvement using clinical indicators: the Danish National Indicator Project. *Int J Qual Health Care* 2004 April;16 Suppl 1:i45-i50.**

(101) **Statistics Denmark. *Statistics Denmark's Classification of Occupational Skills*. 1 ed. Copenhagen: 1996.**

(102) **Kondrup J, Allison SP, Elia M, Vellas B, Plauth M. ESPEN guidelines for nutrition screening 2002. *Clin Nutr* 2003 August;22(4):415-21.**

(103) **Royston P. Multiple imputation of missing values. *The Stata Journal 4* 2004;227-41.**

(104) **Royston P. Multiple imputation of missing values: update. *The Stata Journal 5* 2005;188-201.**

(105) **Royston P. Multiple imputation of missing values: update of ice. *The Stata Journal 5* 2005;527-36.**

(106) **White IR, Royston P. Imputing missing covariate values for the Cox model. *Stat Med* 2009 July 10;28(15):1982-98.**

(107) **Rothman KJ. *Epidemiology*
an introduction. Oxford: Oxford University Press; 2002.**

(108) **van SA, Reitsma JB, Limburg M, van den Bos GA, de Haan RJ. Impact of stroke type on survival and functional health. *Cerebrovasc Dis* 2001;12(1):27-33.**

(109) **Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med* 1994 July 11;154(13):1449-57.**

(110) Rothwell PM, Coull AJ, Silver LE, Fairhead JF, Giles MF, Lovelock CE, Redgrave JN, Bull LM, Welch SJ, Cuthbertson FC, Binney LE, Gutnikov SA, Anslow P, Banning AP, Mant D, Mehta Z. Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study). *Lancet* 2005 November 19;366(9499):1773-83.

(111) Thorvaldsen P, Davidsen M, Bronnum-Hansen H, Schroll M. Stable stroke occurrence despite incidence reduction in an aging population: stroke trends in the danish monitoring trends and determinants in cardiovascular disease (MONICA) population. *Stroke* 1999 December;30(12):2529-34.

(112) Danmarks Statistik. Befolkningsfremskrivninger 2009-2050. Befolkning og Valg. [Nr 228]. 2010. Ref Type: Generic

Appendix 1

Standarder, indikatorer og prognostiske[1] faktorer for apopleksi i Det Nationale Indikatorprojekt

INDIKATOROMRÅDER	INDIKATORER	TYPE	STANDARD	TIDSRAMME
ORGANISERING AF BEHANDLING OG REHABILITERING I EN APOPLEKSIENHED	Andel patienter, der indlægges i en apopleksienhed	Proces	Mindst 90 % med akut apopleksi indlægges i en apopleksienhed	Senest 2. indlæggelsesdøgn
MEDIKAMENTEL SEKUNDÆR PROFYLAKSE	Andel patienter med akut iskæmisk apopleksi uden atrieflimren, der sættes i trombocythæmmerbehandling	Proces	MIndst 95 % med akut iskæmisk apopleksi uden atrieflimren sættes i behandling med trombocythæmmer	Senest 2. indlæggelsesdøgn
	Andel patienter med akut iskæmisk apopleksi og atrieflimren, der sættes i antikoagulansbehandling	Proces	Mindst 60 % med akut iskæmisk apopleksi og atrieflimren sættes i antikoagulations-behandling	Senest 14 dage efter indlæggelsen
DIAGNOSTICERING VED CT / MR SCANNING	Andel patienter, der får udført CT / MR scanning	Proces	Mindst 90 % får udført CT / MR scanning	Senest 2. indlæggelsesdøgn
VURDERING VED FYSIOTERAPEUT	Andel patienter, der af fysioterapeut vurderes med henblik på rehabilitering	Proces	Mindst 90 % vurderes med henblik på rehabilitering	Senest 2. indlæggelsesdøgn
VURDERING VED ERGOTERAPEUT	Andel patienter, der af ergoterapeut vurderes med henblik på rehabilitering	Proces	Mindst 90 % vurderes med henblik på rehabilitering	Senest 2. indlæggelsesdøgn
VURDERING AF ERNÆRINGSRISIKO	Andel patienter, der får vurderet ernæringsrisiko	Proces	Mindst 90 % får vurderet ernæringsrisiko	Senest 2. indlæggelsesdøgn
LETALITET	Andel patienter, der dør indenfor den første måned efter apopleksiens opståen	Resultat	Max. 20 % må dø inden for den første måned efter apopleksiens opståen	30 dage, 3, 6, 12 måneder efter apopleksiens opståen

[1] Ved sammenligninger over tid eller mellem afdelinger vil der blive korrigeret for evt. forskelle i fordeling af en række prognostiske faktorer. Se beskrivelsen af disse på side 13.

Appendix 2

Standarder, indikatorer og prognostiske[2] faktorer for apopleksi i Det Nationale Indikatorprojekt

INDIKATOROMRÅDER	INDIKATORER	TYPE	STANDARD	TIDSRAMME
Organisering af behandling og rehabilitering i en apopleksienhed	Andel patienter, der indlægges i en apopleksienhed	Proces	Mindst 90 % med akut apopleksi indlægges i en apopleksienhed	Senest 2. indlæggelsesdøgn
Medikamentel sekundær profylakse	Andel patienter med akut iskæmisk apopleksi uden atrieflimren, der sættes i trombocythæmmerbehandling	Proces	MIndst 95 % med akut iskæmisk apopleksi uden atrieflimren sættes i behandling med trombocythæmmer	Senest 2. indlæggelsesdøgn
	Andel patienter med akut iskæmisk apopleksi og atrieflimren, der sættes i antikoagulansbehandling	Proces	Mindst 95 % med akut iskæmisk apopleksi og atrieflimren sættes i antikoagulations-behandling	Senest 14 dage efter indlæggelsen
Diagnostisering ved CT / MR scanning	Andel patienter, der får udført CT / MR scanning	Proces	Mindst 90 % får udført CT / MR scanning	1. indlæggelsesdøgn[2]
Vurdering ved fysioterapeut	Andel patienter, der af fysioterapeut vurderes med henblik på rehabilitering	Proces	Mindst 90 % vurderes med henblik på rehabilitering	Senest 2. indlæggelsesdøgn
Vurdering ved ergoterapeut	Andel patienter, der af ergoterapeut vurderes med henblik på rehabilitering	Proces	Mindst 90 % vurderes med henblik på rehabilitering	Senest 2. indlæggelsesdøgn
Vurdering af ernæringsrisiko	Andel patienter, der får vurderet Ernæringsrisiko	Proces	Mindst 90 % får vurderet ernæringsrisiko	Senest 2. indlæggelsesdøgn
Mortalitet	Andel patienter, der dør indenfor 30 dage efter indlæggelse med apopleksi	Resultat	Max. 20 % må dø indenfor 30 dage efter indlæggelse med apopleksi	30 dage efter indlæggelse

[2] Ved sammenligninger over tid eller mellem afdelinger vil der blive korrigeret for evt. forskelle i fordeling af en række prognostiske faktorer. Se beskrivelsen af disse på side 14.

2 Anbefalet tidsramme i Referenceprogram for behandling af patienter med apopleksi er 24 timer. P.g.a. manglende registrering af klokkeslæt i NIP-apopleksi foretages indikatorværdi beregning både i forhold til tidsrammerne "senest 1. indlæggelsesdøgn" og "senest 2. indlæggelsesdøgn".

Appendix 3

Standarder, indikatorer og prognostiske[1] faktorer for apopleksi i Det Nationale Indikatorprojekt

INDIKATOROMRÅDER	INDIKATORER	TYPE	STANDARD	TIDSRAMME
Organisering af behandling og rehabilitering i en apopleksienhed	Andel patienter, der indlægges i en apopleksienhed	Proces	Mindst 90 % med akut apopleksi bliver indlagt i en apopleksienhed	Senest 2. indlæggelsesdøgn
Medikamentel sekundær profylakse	Andel patienter med akut iskæmisk apopleksi uden atrieflimren, der sættes i trombocythæmmerbehandling	Proces	Mindst 95 % med akut iskæmisk apopleksi uden atrieflimren bliver sat i behandling med trombocythæmmer	Senest 2. indlæggelsesdøgn
	Andel patienter med akut iskæmisk apopleksi og atrieflimren, der sættes i antikoagulansbehandling	Proces	Mindst 95 % med akut iskæmisk apopleksi og atrieflimren bliver sat i antikoagulations-behandling	Senest 14 dage efter indlæggelsen
Diagnostisering ved CT/ MR scanning	Andel patienter, der får udført CT / MR scanning	Proces	Mindst 80 % får udført CT / MR scanning	På indlæggelsesdagen
Vurdering ved fysioterapeut	Andel patienter, der af fysioterapeut vurderes med henblik på afklaring af omfang og type af rehabilitering samt tidspunkt for opstart af fysioterapi	Proces	Mindst 90 % bliver vurderet med henblik på rehabilitering	Senest 2. indlæggelsesdøgn
Vurdering ved ergoterapeut	Andel patienter, der af ergoterapeut vurderes med henblik på afklaring af omfang og type af rehabilitering samt tidspunkt for opstart af ergoterapi	Proces	Mindst 90 % bliver vurderet med henblik på rehabilitering	Senest 2. indlæggelsesdøgn
Vurdering af ernæringsrisiko	Andel patienter, der får vurderet ernæringsrisiko	Proces	Mindst 90 % får vurderet ernæringsrisiko	Senest 2. indlæggelsesdøgn
Vurdering med vandtest	Andel patienter, der vurderes med vandtest inden indtagelse af oral føde eller væske med henblik på synkefunktion og aspirationsrisiko	Proces	Mindst 90 % bliver vurderet med vandtest med henblik på synkefunktion og aspirationsrisiko	På indlæggelsesdagen
Ultralyd/CT-angiografi af halskar	Andel patienter, der får foretaget ultralyd/CT-angiografi af halskar	Proces	Mindst 90 % får foretaget ultralyd/ CT-angiografi af halskar.	Senest 4. indlæggelsesdøgn
Mortalitet	Andel patienter, der dør indenfor 30 dage efter indlæggelse med apopleksi	Resultat	Max. 15 % må dø indenfor 30 dage efter indlæggelse med apopleksi	30 dage efter indlæggelse

[1] Ved sammenligninger af mortalitet over tid eller mellem afdelinger vil der blive korrigeret for evt. forskelle i fordeling af en række prognostiske faktorer.

Age and Ageing Advance Access published October 25, 2007

Age and Ageing
doi:10.1093/ageing/afm134

Older patients with acute stroke in Denmark: quality of care and short-term mortality. A nationwide follow-up study

KAARE DYRE PALNUM[1], PALLE PETERSEN[2], HENRIK TOFT SØRENSEN[1], ANETTE INGEMAN[3], JAN MAINZ[3], PAUL BARTELS[3], SØREN PAASKE JOHNSEN[1]

[1]Department of Clinical Epidemiology, Aarhus University Hospital, Ole Worms Allé 1150, 8000 Aarhus C, Denmark
[2]Department of Neurology, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen Ø, Denmark
[3]The Coordinating Secretariat (NIP), County of Aarhus, Lyseng Allé 1, 8270 Hojbjerg, Denmark

Address correspondence to: Kaare Dyre Palnum. Tel: +45 8942 4808; Fax: +45 8942 4801. Email: kdp@dce.au.dk

Abstract

Background and purpose: age may predict level of care and subsequent outcome among patients with stroke. We examined fulfilment of quality-of-care criteria according to age and the possible impact of any age-related differences on short-term mortality in a population-based nationwide follow-up study in Denmark.
Methods: we identified 29,549 patients admitted with stroke between January 2003 and October 2005 in the Danish National Indicator Project (DNIP). Data on 30- and 90-day mortality were obtained from the Civil Registration System. We compared proportions of patients receiving adequate care across age groups, as measured by admission to a specialised stroke unit, administration of antiplatelet or anticoagulant therapy, examination with CT/MR scan, assessment by a physiotherapist and an occupational therapist, or assessment of nutritional risk. Further, we estimated 30- and 90-day mortality rate ratios (MRRs) across age groups, adjusted for fulfilment of quality-of-care criteria and patient characteristics.
Results: the proportion of eligible patients who received adequate care declined with age for all the examined processes. The relative risk (RR) of receiving specific components of care ranged from 0.66 (95% confidence interval (CI): 0.60–0.73) to 0.97 (95% CI: 0.95–0.99) when comparing patients >80 years of age with patients ≤65 years of age. Although mortality increased with age, adjusting for the age-related differences in care did not alter the magnitude of the increase.
Conclusions: elderly stroke patients in Denmark receive a lower quality of care than do younger stroke patients, however, the age-related differences are modest for most examined quality-of-care criteria and do not appear to explain the higher mortality among older patients.

Keywords: *quality of care, prognosis, elderly, stroke*

Introduction

Advanced age is associated not only with primary stroke but also with increased mortality and a reduced functional status after the stroke [1–3]. There have been few attempts to clarify the association between the age, quality of care and outcomes of stroke, but studies have reported age-related differences in care. Older patients, typically starting from age 65 years, seem to receive fewer relevant evidence-based diagnostic examinations and less care [4, 5] than do younger patients. Uncertainty remains, however, about the magnitude and implications for the outcomes of stroke of these possible age-related differences. The existing studies were based on selected patient populations, lacked detailed data on diagnosis and care (in particular, the timing of specific interventions), and had incomplete follow-up. Furthermore, these studies have not examined to which extent the possible differences in the quality of care could explain the higher mortality among older patients with stroke.

We aimed to explore whether age-related differences in care occur, and, if so, to assess whether they affect short-term mortality. We, therefore, examined the quality of care and mortality according to age in a nationwide population-based follow-up study of Danish patients with stroke.

Methods

The Danish National Indicator Project (DNIP)

The Danish National Health Service provides tax-supported health care to the country's 5 million residents, all of whom have free access to hospital care. The Danish National Indicator Project (DNIP) is a nationwide initiative to monitor and improve the quality of care for specific diseases, including stroke [6]. The project does this by focusing on the development and implementation of evidence-based indicators related to the structure, process and outcome of health care and, subsequently, by monitoring the fulfilment of these indicators. Participation in the project is mandatory for all hospital departments treating patients with stroke.

Study population

We identified all admissions with acute stroke registered in DNIP from 13 January 2003 to 1 November 2005 ($n = 31{,}157$). All patients ($\geq$18 years of age) admitted to Danish hospitals with acute stroke according to the WHO criteria (i.e. rapidly developed clinical signs of focal or global disturbance of cerebral function, lasting more than 24 h or until death, with no apparent non-vascular cause [7]) are eligible for inclusion in DNIP. Patients with subdural hematoma, epidural or subarachnoidal hemorrhage, retinal infarct, and infarct caused by trauma, infection, surgery or an intracerebral malign process are not included. For this study, we only included the first stroke event registered during the study period. Furthermore, only patients with a valid civil registry number (a unique personal identification number allowing unambiguous linkage between various public registers) residing in Denmark, and therefore, eligible for follow-up were included. A total of 29,549 patients (94.8% of the original patient population) were included.

Quality-of-care criteria

A national expert panel including physicians, nurses, physiotherapists and occupational therapists identified seven quality-of-care criteria covering the acute phase of stroke based on systematic search of the scientific literature [6]: admission to a specialised stroke unit, antiplatelet therapy initiated among patients with ischemic stroke without atrial fibrillation, oral anticoagulant therapy initiated among patients with ischemic stroke and atrial fibrillation, examination with CT/MRI scan, assessment by a physiotherapist, assessment by an occupational therapist and assessment of nutritional risk. A time frame was defined for each criterion to capture the timeliness of the interventions. The time frame was the second day of hospitalisation for all criteria, except initiation of oral anticoagulant therapy where the time frame was the 14th day of hospitalisation.

Assessment by a physiotherapist and occupational therapist was defined as a formal bedside assessment of the patient's need for rehabilitation, whereas assessment of nutritional risk was defined as an assessment following the recommendations of the European Society for Parenteral and Enteral Nutrition, i.e. calculation of a score which both accounts for the nutritional status and for the stress induced by the stroke [8].

Upon hospital admission, data on care, and prognostic factors for short-term mortality were collected for each patient using a standardised form. After hospital discharge the data were entered into a central database. Patients were classified as eligible or non-eligible for the specific processes of care depending on whether the stroke team or physician treating the patient identified contraindications, e.g. severe dementia in a patient with ischemic stroke and atrial fibrillation precluding oral anticoagulant therapy, or rapid spontaneous recovery of motor symptoms making early assessment by a physiotherapist and occupational therapist irrelevant.

Thus, it was left to the staff to decide whether or not contraindications to the specific criteria were present.

Prognostic factors for short-term mortality

Data on prognostic factors included age, sex, marital status (living with partner, family or friend, living alone), housing (own home, nursing home or other form of institution), Scandinavian Stroke Scale score, history of stroke or myocardial infarction, previous and/or current atrial fibrillation, hypertension, diabetes mellitus or intermittant claudication, smoking habits (smoker, ex-smoker, never), and alcohol intake ($\leq$14/21, $>$14/21 drinks per week for women and men, respectively).

Statistical analysis

First we calculated, in each age group, proportions of patients receiving adequate care, as defined by fulfilment of the quality-of-care criteria. The age groups were defined to allow for comparison with the existing studies. The proportions were compared using patients aged $\leq$65 years of age as reference, and relative risks (RRs) were computed for each age group. Secondly, we computed 30- and 90-day mortality rates according to age. We used Cox's proportional hazards regression to obtain mortality rate ratios (MRRs) for time to death within 30 or 90 days after stroke, according to age, while adjusting for potential confounders of the association between age and mortality i.e. fulfilment of quality-of-care criteria and prognostic factors. Follow-up time started on the date of hospital admission for stroke and ended on date of death, emigration, or after 30 (or 90) days, whichever came first. We first computed the MRRs according to age, while adjusting for fulfilment of each of the quality-of-care criteria and prognostic factors. In order to include all of the quality-of-care criteria in the same analysis, we then restricted the analysis to patients without contraindications to any of the quality-of-care criteria. As the criteria on antiplatelet and oral anticoagulant therapy were mutually exclusive, we combined these two indicators into a combined criterion (antiplatelet or anticoagulant therapy) in the latter analysis.

We analysed data using STATA version 9.0 (StataCorp, College Station, Texas, USA).

Results

Table 1 shows characteristics of the 29,549 patients according to age groups. Increasing age was associated with a more adverse prognostic profile, including atrial fibrillation, previous myocardial infarction and stroke; likewise, the proportion of patients with severe stroke increased with age.

Fulfilment of quality-of-care criteria

Table 2 displays, according to age, the proportions of patients which fulfilled the quality-of-care criteria. The varying number of patients included in the analysis of the specific criteria reflect that a varying proportion of the patients was eligible for the individual criteria, e.g. in 6,141 out of 8,580 patients aged 65 years or younger platelet inhibitor therapy was considered to be indicated as the patients had an ischemic or unspecified stroke and no contraindications for platelet inhibitory therapy, and of these, 4,719 received the treatment within 2 days after hospitalisation. The proportion of eligible patients who fulfilled the quality-of-care criteria declined with age for all the examined processes. The oldest patients (>80 years) were in all analyses least likely to fulfil the quality-of-care criteria. In this age group, the RR for receiving specific components of care ranged from 0.66 (95% CI: 0.60–0.73) to 0.97 (95% CI: 0.95–0.99) when compared with patients aged ≤65 years of age. However, the RR remained above 0.90 for all quality-of-care criteria except for treatment with oral anticoagulants (0.66 (95% CI: 0.60–0.73)) and early assessment of nutritional risk (0.78 (95% CI: 0.76–0.82)), respectively.

A total of 12,744 patients were found eligible for all quality-of-care criteria, e.g. the patients had no contraindications to any of the processes of care. Age-related differences in care were also found in this subgroup, i.e. 23.7, 21.4 and 16.5% of patients aged ≤65, >65–80 and >80 years of age, respectively, fulfilled all the quality-of-care criteria.

30 and 90-day cumulative mortality

Mortality increased with age: the cumulative 30-day mortality was 5.3, 9.7 and 19.4% among patients aged ≤65, >65–80 and >80 years of age, respectively. As expected, we found a reduction of the MRRs after adjustment for a wide range of prognostic factors, including socio-demographic and clinical characteristics (Table 3). However, further adjustment for age-related differences in fulfilment of the examined quality-of-care criteria had no or only a minor effect on the age-related differences in mortality. Conducting these analyses for the outcome of 90-day mortality produced the same pattern (data not shown).

Among the 12,744 patients who were eligible for all quality-of-care criteria, the age-related differences in both 30- and 90-day mortality were also present and likewise remained unaltered by accounting for the age-related differences in fulfilment of the quality-of-care criteria: the MMRs for 30 days changed from 1.70 (1.26–2.31) to 1.70 (1.25–2.31) and 2.89 (2.10–3.97) to 2.82 (2.06–3.88) for patients aged >65–80 and >80 years of age, respectively.

Discussion

In this large nationwide follow-up study, we found an inverse association between age and quality of care. However, the age-related differences in quality of care were substantial only for two quality-of-care criteria—oral anticoagulant therapy and early evaluation of nutritional status—and they did not appear to explain age-related differences in mortality.

The main strength of our study is its prospective population-based design, complete long-term follow-up, negligible selection bias and low risk of information bias. Further, our analyses were based on a large cohort, with detailed data on a range of specific processes of care; only patients without contraindications for the specific processes of care were included in the analyses. Furthermore, while examining mortality, we reduced confounding by adjusting for a wide range of prognostic factors.

Use of data collected in a non-standardised setting during routine clinical work is a limitation of this study, potentially affecting accuracy of collected data. At the same time, participation in DNIP is mandatory for all departments treating patients with acute stroke in Denmark, and extensive efforts are made to ensure the validity of DNIP [6]. In particular, a regular structured audit is conducted nationally, regionally and locally, and includes validation of the completeness of patient registration against county hospital discharge registries. Furthermore, any misclassification of data on care in DNIP is unlikely to depend on age and thus, if present, would lessen our ability to detect age-related differences in quality of care and result in conservative RR estimates.

Although we adjusted for a wide range of prognostic factors, we cannot entirely exclude the possibility that our results may still be influenced by residual confounding due to the use of crude variables (e.g. data on levels of hypertension were not available) or unaccounted confounding from factors not included in the analyses (e.g. mental function). The prevalence of patients with missing data on the prognostic factors ranged between 5 and 30% for the variables considered. Although missing data should always be a reason for concern, we have no reason to believe that this had any substantial influence on our findings, which remained virtually unchanged whether or not patients with missing data were included in the analyses.

We used mortality as the clinical end-point. Despite its obvious importance, mortality is certainly not the only end-point relevant for patients with stroke. Examination of the possible effect of age-related differences in quality of care on other end-points, e.g. functional level after discharge would of course also be highly relevant. Unfortunately, such data were not available in our study.

Our findings are in accordance with those from other studies [4, 5, 9]. In a joint European study, Bhalla *et al.* found a less intensive effort for diagnosis, care and rehabilitation of patients aged ≥75 years compared with patients aged <75 years, as manifested by lower proportions of them examined with CT scan (87 versus 79%) or echocardiography

Table 1. Descriptive characteristics of 29,549 patients with acute stroke registered in the Danish National Indicator Project, 2003–2005

	≤ 65 (n = 8,580) (%)	>65–80 (n = 12,474) (%)	>80 (n = 8,495) (%)
Sex			
Female	3,083 (35.9)	5,733 (46.0)	5,361 (63.1)
Male	5,497 (64.1)	6,741 (54.0)	3,134 (36.9)
Comorbidity			
Diabetes mellitus			
Yes	1,140 (13.3)	1,803 (14.5)	914 (10.8)
No	6,816 (79.9)	9,667 (77.5)	6,758 (79.6)
Missing	543 (6.3)	865 (6.9)	742 (8.7)
Atrial fibrillation			
Yes	454 (5.3)	1,948 (15.6)	2,370 (27.9)
No	7,436 (86.7)	9,379 (75.2)	5,254 (61.8)
Undisclosed	603 (7.0)	1,002 (8.0)	787 (9.3)
AMI			
Yes	568 (6.6)	1,380 (11.1)	839 (9.9)
No	7,342 (85.6)	9,896 (79.3)	6,553 (77.1)
Missing	588 (6.8)	1,058 (8.5)	1,015 (11.9)
Hypertension			
Yes	3,416 (39.8)	5,745 (46.1)	3,486 (41.0)
No	4,430 (51.6)	5,425 (43.5)	3,870 (45.6)
Missing	659 (7.7)	1,175 (9.4)	1,056 (12.4)
Former stroke			
Yes	1,785 (20.8)	3,535 (28.3)	2,274 (26.8)
No	6,189 (72.1)	7,936 (63.6)	5,357 (63.1)
Missing	523 (6.1)	876 (7.0)	784 (9.2)
Intermittant claudication			
Yes	254 (3.0)	581 (4.7)	247 (2.9)
No	7,250 (84.5)	9,742 (78.1)	6,251 (73.6)
Missing	967 (11.3)	1,967 (15.8)	1,889 (22.2)
Stroke severity (SSS)			
Very severe (0–14 pt)	627 (7.3)	1,250 (10.0)	1,395 (16.4)
Severe (15–29 pt)	586 (6.8)	1,131 (9.1)	1,003 (11.8)
Moderate (30–44 pt)	1,111 (12.9)	2,110 (16.9)	1,866 (22.0)
Mild (45–58 pt)	5,024 (58.6)	6,205 (49.7)	2,874 (33.8)
Smoking			
Smoker	4,492 (52.4)	4,210 (33.8)	1,309 (15.4)
Ex-smoker (more than 6 months)	1,130 (13.2)	2,577 (20.7)	1,373 (16.2)
Never smoked	1,880 (21.9)	3,368 (27.0)	3,147 (37.0)
Undisclosed	970 (11.3)	2,131 (17.1)	2,556 (30.1)
Alcohol intake			
14/21 drinks/week or less	6,258 (72.3)	9,487 (76.1)	6,067 (71.4)
More than 14/21 drinks/week	1,131 (13.2)	664 (5.3)	102 (1.2)
Undisclosed	1,080 (12.6)	2,132 (17.1)	2,229 (26.2)
Type of residence			
Own residence	7,531 (87.8)	10,639 (85.3)	6,333 (74.5)
Care home	137 (1.6)	602 (4.8)	1,321 (15.5)
Other	167 (1.9)	190 (1.5)	167 (2.0)
Missing	646 (7.5)	882 (7.1)	572 (6.7)
Civil status			
Cohabitant	5,660 (66.0)	6,701 (53.7)	2,379 (28.0)
Lives alone	2,247 (26.2)	4,739 (38.0)	5,126 (60.4)
Other	128 (1.5)	215 (1.7)	438 (5.2)
Missing	459 (5.3)	673 (5.4)	463 (5.5)

(34 versus 17%), a lesser physio- and ergotherapeutical effort, and lower rates of transfer to rehabilitation ward upon discharge [4]. In another prospective joint European study on 4,499 patients with stroke from 12 specialised centres, Di Carlo *et al.* found that brain imaging and other diagnostic tools were less frequently utilised in the older patients, whereby merely 66.9% of older patients received brain imaging compared with 87.7% of younger patients.

Table 2. Fulfilment of quality-of-care criteria according to age

Fulfilment of quality-of-care criteria	≤ 65 years (%) *n* = 8 580	RR (reference)	>65–80 years (%) *n* = 12 474	RR (95% CI)	>80 years (%) *n* = 8 495	RR (95% CI)
Treatment/rehabilitation in stroke unit	1,954/6,576 (77.1)	1.0	2,904/9,472 (76.5)	0.99 (0.98–1.01)	2,124/6,308 (74.9)	0.97 (0.95–0.99)
Antiplatelet therapy	1,422/4,719 (76.8)	1.0	2,028/5,688 (73.7)	0.96 (0.94–0.98)	1,239/2,920 (70.2)	0.91 (0.89–0.94)
Oral anticoagulant therapy	102/199 (66.1)	1.0	490/736 (60.0)	0.91 (0.82–0.99)	674/526 (43.8)	0.66 (0.60–0.73)
CT/MRI scan	1,359/6,895 (83.5)	1.0	2,466/9,521 (79.4)	0.95 (0.93–0.96)	1,766/6,301 (78.1)	0.93 (0.92–0.95)
Assessment by a physiotherapist	3,214/3,237 (50.2)	1.0	4,964/5,025 (50.3)	1.00 (0.97–1.03)	3,627/3,211 (47.0)	0.94 (0.90–0.97)
Assessment by an occupational therapist	3,603/2,910 (44.8)	1.0	5,564/4,401 (44.2)	0.99 (0.95–1.02)	3,871/2,838 (42.3)	0.95 (0.91–0.98)
Nutritional risk evaluation	2,661/3,163 (54.3)	1.0	4,364/4,267 (49.4)	0.91 (0.88–0.94)	3,261/2,432 (42.7)	0.78 (0.76–0.82)

Table 3. Mortality rate ratios (MRR) during 30 days, according to age. Adjusted for fulfilment of quality-of-care criteria and prognostic factors

Quality-of-care criterion	Number (*n*)	Age	Absolute mortality (%)	Crude MRR (95% CI)	Adj. MRR[a] (95% CI)	Fully adj. MRR[b] (95% CI)
Treatment/rehabilitation in stroke unit	29,338	≤ 65	443/8,530 (5.2)	1.00	1.00	1.00
		>65–80	1,197/12,376 (9.7)	1.90 (1.70–2.12)	1.52 (1.33–1.72)	1.52 (1.34–1.73)
		>80	1,638/8,432 (19.4)	3.97 (3.58–4.41)	2.03 (1.78–2.32)	2.05 (1.80–2.35)
Antiplatelet therapy	18,016	≤ 65	127/6,141 (2.1)	1.00	1.00	1.00
		>65–80	319/7,716 (4.1)	2.01 (1.64–2.48)	1.57 (1.25–1.97)	1.55 (1.24–1.95)
		>80	398/4,159 (9.6)	4.78 (3.91–5.84)	2.63 (2.07–3.34)	2.62 (2.06–3.33)
Oral anticoagulant therapy	2,727	≤ 65	10/301 (3.3)	1.00	1.00	1.00
		>65–80	97/1,226 (7.9)	2.43 (1.27–4.66)	2.37 (1.12–5.02)	2.27 (1.07–4.82)
		>80	207/1,200 (17.3)	5.54 (2.94–10.45)	3.84 (1.81–8.15)	3.34 (1.57–7.12)
CT/MRI scan	28,308	≤ 65	430/8,254 (5.2)	1.00	1.00	1.00
		>65–80	1,113/11,987 (9.3)	1.82 (1.62–2.03)	1.43 (1.26–1.63)	1.44 (1.26–1.64)
		>80	1,477/8,067 (18.3)	3.71 (3.33–4.14)	1.90 (1.66–2.18)	1.92 (1.68–2.19)
Assessment by a physiotherapist	23,277	≤ 65	184/6,451 (2.9)	1.00	1.00	1.00
		>65–80	634/9,988 (6.3)	2.26 (1.92–2.67)	1.68 (1.41–2.02)	1.70 (1.42–2.03)
		>80	921/6,838 (13.5)	4.95 (4.22–5.79)	2.46 (2.04–2.97)	2.48 (2.06–2.99)
Assessment by an occupational therapist	23,187	≤ 65	172/6,513 (2.6)	1.00	1.00	1.00
		>65–80	595/9,965 (6.0)	2.30 (1.94–2.72)	1.71 (1.42–2.07)	1.72 (1.43–2.08)
		>80	875/6,709 (13.0)	5.16 (4.38–6.08)	2.58 (2.12–3.13)	2.60 (2.15–3.17)
Nutritional risk evaluation	20,148	≤ 65	165/5,824 (2.8)	1.00	1.00	1.00
		>65–80	532/8,631 (6.2)	2.21 (1.86–2.63)	1.61 (1.33–1.95)	1.61 (1.32–1.95)
		>80	781/5,693 (13.7)	5.08 (4.29–6.01)	2.43 (1.99–2.97)	2.43 (1.99–2.97)

[a] Adjusted for prognostic factors (gender, civil status, type of residence, stroke severity, former stroke, AMI, atrial fibrillation, hypertension, diabetes, intermittant claudication, smoking and alcohol).
[b] Adjusted for fulfilment of the specific quality-of-care criterion and prognostic factors.

Recently, Fairhead and Rothwell reported a lower use of carotid imaging and carotid endarterectomy in routine clinical practice in patients aged ≥ 80 years of age with transient ischaemic attack or ischaemic stroke [9].

The 30-day mortality found in our study is consistent with the findings of Di Carlo *et al.*, who found a 28-day mortality of 10.0% among patients <80 years of age compared with 20.8% among patients ≥80 years of age. However, to our knowledge, no existing study has investigated whether this difference in mortality could be explained by the age-related differences in quality of care. Taking these differences into account had very little impact on the MMRs in our study, indicating that the differences in the examined processes of care are not major contributors to the higher mortality among the elderly.

Age-related differences in the quality of care have also been reported within other medical specialities [10–15]. The phenomenon is commonly referred to as 'ageism'. A central aspect in the struggle against ageism is to get a clearer picture of the scope and consequences of age-related differential treatment. In this context, it is important to be aware that in some situations there are good ethical and clinical reasons

for treating elderly patients different, e.g. severe comorbidity or inability to comply with the recommended treatment. It is essential that studies of age-related differences take these aspects into account, in order to avoid overestimating or misinterpreting the observed differences thus hindering the effort of effective elimination of true ageism.

In conclusion, we found that elderly stroke patients in Denmark, in particular those older than 80 years of age, receive a poorer quality of care than do younger patients. The largest age-related differences were found for early anticoagulant therapy and early assessment of nutritional risk. However, the differences in the quality of care were not substantial for most of the examined processes. The rather small age-related differences found in the examined processes of care did not appear to explain the higher mortality among the elderly. Continuous efforts are warranted in order to ensure patients with stroke optimal care irrespective of age.

Key points

- Elderly patients with stroke in Denmark, in particular, those over the age of 80 years of age, receive a lower quality of care than do younger patients.
- The age-related differences were minor for most examined processes of care except for early anticoagulant therapy and early assessment of nutritional risk.
- Age-related differences of the examined processes of care did not appear to explain the higher mortality among elderly stroke patients.

Conflicts of interest disclosures

None

Funding

Supported by grants from the Foundation for Research in Neurology and The Aarhus University Research Foundation.

References

1. Warlow C. Stroke a Practical Guide to Management, 2nd edition. Oxford: Blackwell Science, 2001.
2. Stevens A. Health Care needs Assessment the Epidemiologically Based Needs Assessment Reviews, 2nd edition. Oxford: Radcliffe, 2004.
3. Kwakkel G, Wagenaar RC, Kollen BJ *et al.* Predicting disability in stroke–a critical review of the literature. Age Ageing 1996; 25: 479–89.
4. Bhalla A, Grieve R, Tilling K *et al.* Older stroke patients in Europe: stroke care and determinants of outcome. Age Ageing 2004; 33: 618–24.
5. Di CA, Lamassa M, Pracucci G *et al.* Stroke in the very old: clinical presentation and determinants of 3-month functional outcome: A European perspective. European BIOMED Study of Stroke Care Group. Stroke 1999; 30: 2313–9.
6. Mainz J, Krog BR, Bjornshave B *et al.* Nationwide continuous quality improvement using clinical indicators: The Danish National Indicator Project. Int J Qual Health Care 2004; 16(Suppl. 1): i45–50.
7. The World Health Organization. MONICA project (monitoring trends and determinants in cardiovascular disease): a major international collaboration. WHO MONICA Project Principal Investigators. J Clin Epidemiol 1988; 41: 105–14.
8. Kondrup J, Allison SP, Elia M *et al.* ESPEN guidelines for nutrition screening 2002. Clin Nutr 2003; 22: 415–21.
9. Fairhead JF, Rothwell PM. Underinvestigation and undertreatment of carotid disease in elderly patients with transient ischaemic attack and stroke: comparative population based study. BMJ 2006; 333: 525–7.
10. Peake MD, Thompson S, Lowe D *et al.* Ageism in the management of lung cancer. Age Ageing 2003; 32: 171–7.
11. Regueiro CR, Gill N, Hart A *et al.* Primary angioplasty in acute myocardial infarction: does age or race matter? J Thromb Thrombolysis 2003; 15: 119–23.
12. Bond M, Bowling A, McKee D *et al.* Does ageism affect the management of ischaemic heart disease? J Health Serv Res Policy 2003; 8: 40–7.
13. Woodard S, Nadella PC, Kotur L *et al.* Older women with breast carcinoma are less likely to receive adjuvant chemotherapy: evidence of possible age bias? Cancer 2003; 98: 1141–9.
14. Jerant AF, Franks P, Jackson JE *et al.* Age-related disparities in cancer screening: analysis of 2001 behavioral risk factor surveillance system data. Ann Fam Med 2004; 2: 481–7.
15. O'Connell JB, Maggard MA, Ko CY. Cancer-directed surgery for localized disease: decreased use in the elderly. Ann Surg Oncol 2004; 11: 962–9.

Received 30 November 2006; accepted in revised form 26 July 2007

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Stroke Association
A Division of American Heart Association

Sex-Related Differences in Quality of Care and Short-Term Mortality Among Patients With Acute Stroke in Denmark: A Nationwide Follow-Up Study

Kaare D. Palnum, Grethe Andersen, Annette Ingeman, Birgitte R. Krog, Paul Bartels and Søren P. Johnsen

Stroke 2009;40;1134-1139; originally published online Feb 10, 2009;
DOI: 10.1161/STROKEAHA.108.543819
Stroke is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0039-2499. Online ISSN: 1524-4628

Sex-Related Differences in Quality of Care and Short-Term Mortality Among Patients With Acute Stroke in Denmark

A Nationwide Follow-Up Study

Kaare D. Palnum, MD; Grethe Andersen, MD, Dr Med Sci; Annette Ingeman, MHSc; Birgitte R. Krog, MPH; Paul Bartels, MD; Søren P. Johnsen, MD, PhD

Background and Purpose—Sex may predict level of care and successive outcome among patients with stroke. We examined fulfillment of quality of care criteria according to sex and possible impact of any sex-related differences on short-term mortality in a population-based nationwide follow-up study in Denmark.

Methods—We identified 29 549 patients admitted with stroke between January 2003 and October 2005 in the Danish National Indicator Project. Data on 30- and 90-day mortality were obtained from The Civil Registration System. We compared proportions of patients receiving adequate care between sexes, as measured by admission to a specialized stroke unit, administration of antiplatelet or anticoagulant therapy, examination with CT/MRI scan, and assessment by a physiotherapist, an occupational therapist, and of nutritional risk. Further, we computed 30- and 90-day mortality rate ratios (MRR), adjusted for patient characteristics, fulfillment of quality of care criteria, and department.

Results—The proportion of patients who received adequate care was either slightly lower or similar among women when compared to men. The relative risks (RR) of receiving specific components of care ranged from 0.84 (95% confidence interval [CI]:0.74 to 0.96) to 1.01 (95% CI:0.96 to 1.06) when comparing sexes. The adjusted mortality rate ratios were lower among women and adjustment for fulfillment of quality of care criteria had only marginal impact.

Conclusions—There appear not to be any substantial sex-related differences in acute hospital care among patients with stroke in Denmark. The lower female short-term mortality is therefore most likely explained by other factors. **(*Stroke*. 2009;40:1134-1139.)**

Key Words: quality of care ■ prognosis ■ sex ■ stroke

Stroke is a leading cause of mortality among both women and men.[1] Although this disease has many similarities in women and men, a growing body of evidence indicates that differences may exist in treatment, outcome, and prognosis of stroke between sexes.[2–5] Such a pattern has also been reported among other disease entities, in particular among patients with coronary heart disease and congestive heart failure.[6] Existing literature on stroke,[2–5] although not all,[7] suggests that women receive fewer relevant evidence-based diagnostic examinations and less care than men. Uncertainty remains, however, about the magnitude and implications for the outcomes of stroke of these possible sex-related differences. There seems to be a growing need for a better understanding of sex differences in both presentation, progression, treatment, and outcome of stroke.[8] Also, existing literature suggest that older patients, typically starting from age 65 years, seem to receive fewer relevant evidence-based diagnostic examinations and less care,[9–11] however few studies investigating sex differences in treatment and outcome have investigated whether the observed differences can in fact be contributed to age- rather than sex-related differences given the higher mean age of female stroke patients. Also, only few studies had detailed data on diagnosis and care (in particular, the timing of specific interventions) and complete follow-up. Furthermore, none of these studies have examined to which extent the possible differences in the quality of care could have an impact on sex-related differences in mortality.

We aimed to explore whether sex-related differences in care still occur after stratifying by age, and to assess whether they affect short-term mortality. We therefore examined the quality of care and mortality according to sex in a nationwide population-based follow-up study of Danish patients with stroke.

Methods

The Danish National Indicator Project (DNIP)

The Danish National Health Service provides tax-supported health care to the country's 5 million residents, all of whom have free

Received November 22, 2008; accepted December 3, 2008.

From the Department of Clinical Epidemiology (K.D.P., S.P.J.), Aarhus University Hospital, Denmark; the Department of Neurology (G.A.), Aarhus University Hospital, Aarhus Hospital, Denmark; and the Coordinating Secretariat (NIP) (A.I., B.R.K., P.B.), County of Aarhus, Denmark.

Correspondence to Kaare D Palnum, Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, 8200 Aarhus N, Denmark. E-mail kdp@dce.au.dk

Stroke **is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.108.543819**

access to hospital care. DNIP is a nationwide initiative to monitor and improve the quality of care for specific diseases, including stroke.[12] The project does this by developing evidence-based quality criteria related to the structure, process, and outcome of health care and, subsequently, by monitoring the fulfillment of these criteria. Participation in the project is mandatory for all hospital departments in Denmark treating patients with acute stroke.

Study Population

We identified all admissions with acute stroke registered in DNIP from January 13, 2003 to November 1, 2005 (n=31 157 from 41 hospital departments). All patients (≥18 years) admitted to Danish hospitals with acute stroke according to the WHO criteria (ie, rapidly developed clinical signs of focal or global disturbance of cerebral function, lasting more than 24 hours or until death, with no apparent nonvascular cause[13]) are eligible for inclusion in DNIP. Patients with subdural hematoma, epidural or subarachnoidal hemorrhage, retinal infarct, and infarct caused by, trauma, infection, surgery, or an intracerebral malign process are not included. For this study we only included the first stroke event registered during the study period. Furthermore, only patients with a valid civil registry number (a unique personal identification number allowing unambiguous linkage between public registers) residing in Denmark and therefore eligible for follow-up were included. A total of 29 549 patients (94.8% of the original patient population) were included.

Quality of Care Criteria

A national expert panel including physicians, nurses, physiotherapists, and occupational therapists identified 7 quality of care criteria covering the acute phase of stroke based on systematic search of the scientific literature.[12] In the selection of the criteria, the feasibility of collecting the required data in routine clinical settings and the ability of the criteria to reflect the multidisciplinary efforts involved in modern stroke care were also considered. The criteria included early admission to a specialized stroke unit, early administration of antiplatelet or anticoagulant therapy, early examination with CT/MRI scan, and early assessment by a physiotherapist, an occupational therapist, and of nutritional risk.

A time frame was defined for each criterion to capture the timeliness of the interventions. The time frame was the second day of hospitalization for all criteria, except initiation of oral anticoagulant therapy where the time frame was the 14th day of hospitalization. The time frames were in accordance with the principles of the official Danish guidelines for early management of patients with stroke issued by the National Board of Health.[14] The time frames were based on the available scientific evidence which included large scale clinical trials for early administration of antiplatelet therapy but consensus agreement among experts for most of the other processes of care.[15–17]

A specialized stroke unit was defined as a hospital department/unit that exclusively or primarily is dedicated to patients with stroke and which is characterized by multidisciplinary teams, a staff with a specific interest in stroke, involvement of relatives, and continuous education of the staff. Administration of antiplatelet and oral anticoagulant therapy was defined as continuous use of the drugs and not merely a single dose. Assessment by a physiotherapist and occupational therapist was defined as a formal bed-side assessment of the patient's need of rehabilitation, whereas assessment of nutritional risk was defined as an assessment after the recommendations of the European Society for Parenteral and Enteral Nutrition, ie, calculation of a score which both accounts for the nutritional status and for the stress induced by the stroke.[18]

On hospital admission, data on care, and patient characteristics were collected for each patient using a standardized form. After hospital discharge the data were entered into a central database. Patients were classified as eligible or noneligible for the specific processes of care depending on whether the stroke team or physician treating the patient identified contraindications, eg, severe dementia in a patient with ischemic stroke and atrial fibrillation precluding oral anticoagulant therapy, or rapid spontaneous recovery of motor symptoms making early assessment by a physiotherapist and occupational therapist irrelevant. Detailed written instructions were available to the staff which specified criteria for deeming a patient ineligible for the care processes. The reason for deeming a specific patient ineligible was not recorded in the database.

Patient Characteristics

At the time of hospital admission, data were collected on the following characteristics: age, sex, marital status (living with partner, family or friend, living alone), housing (own home, nursing home or other form of institution), Scandinavian Stroke Scale score, history of stroke or myocardial infarction, previous or current atrial fibrillation, hypertension, diabetes mellitus or intermittant claudication, smoking habits (smoker, ex-smoker, never), and alcohol intake (≤14/21, >14/21 drinks per week for women and men, respectively).

We also computed the Charlson comorbidity index score for each patient based on all discharge diagnoses recorded before the stroke hospitalization. The Charlson comorbidity index covers 19 major disease categories, including congestive heart failure, renal disease, and cancer, weighted according to their prognostic impact on patient survival.[19] The index has previously been adapted for use with hospital discharge registry data and has been reported to be useful also among patients with stroke.[20,21] We defined three levels of comorbidity for each patient, based on their complete hospital discharge history, as follows: 0 comorbidities ("none"), 1 to 2 comorbidities ("low"), and >2 comorbidities ("high"). Data on previous hospitalizations were obtained from The National Registry of Patients, which contains data on all discharges from all nonpsychiatric hospitals in Denmark since 1977.

Scandinavian Stroke Scale was used to assess admission stroke severity. The scale is a validated and widely used neurological stroke scale in Scandinavia that evaluates level of consciousness; eye movement; power in the arm, hand, and leg; orientation; aphasia; facial paresis; and gait on a total score that ranges from 0 to 58.[22,23]

Mortality

We computed 30- and 90-day mortality using information from the Civil Registration System. This registry, which is updated daily, keeps electronic records on vital status (dead or alive), date of death, and residence of all Danish citizens. Since 1968, all Danish residents have been assigned a unique civil registration number, which is used in all health databases and permits unambiguous record linkage.[24]

Statistical Analysis

We compared the distribution of patient characteristics between women and men by chi-squared test. To evaluate the quality of care we first calculated, for each sex, the proportion of patients receiving adequate care, both defined as fulfillment of the specific quality of care criteria and as proportion of fulfilled criteria that the patient was deemed eligible for (<50%, 50% to 99% and 100%). Further, we stratified the patients according to age (≤65, >65 to 80 and >80 years) attributable to the sex-specific differences in age distribution and previous reports of age-related differences in care among patients with stroke.[2–4,9–11] The proportions were compared using male sex as reference, and relative risks (RR) were computed for each age group. Secondly, we computed 30-and 90-day mortality rates according to sex. We used Cox proportional hazards regression to obtain mortality rate ratios (MRR) for time to death within 30 or 90 days after stroke, according to sex, while adjusting for potential confounders of the association between sex and mortality ie, patient characteristics, department, and fulfillment of quality of care criteria. Follow-up time started on the date of hospital admission for stroke and ended on date of death, emigration, or after 30 (or 90) days, whichever came first. We corrected for possible clustering by department in all mortality analyses as unmeasured characteristics of the department, including other aspects of quality of care than the criteria examined in this study, might be associated with patient mortality. If this is the case, the mortality of patients treated at the same department is necessarily correlated and conventional statistical analyses may be invalidated. We first computed the unadjusted

Table 1. Descriptive Characteristics of 29 549 Patients With Acute Stroke Registered in the Danish National Indicator Project, 2003 to 2005

	Male (n=15 372)	Female (n=14 177)	*P* Value
Age			
≤65 years	5 497 (35.8 %)	3 083 (21.7 %)	
>65–80 years	6 741 (43.8 %)	5 733 (40.4 %)	
>80 years	3 134 (20.4 %)	5 361 (37.8 %)	< 0.001
Charlson Index			
None (0 pt)	4 087 (26.6%)	3 906 (27.6%)	
Low (1–2 pt)	7 843 (51.0%)	7 211 (50.8%)	
High (>2 pt)	3 442 (22.4%)	3 060 (21.6%)	0.093
Diabetes Mellitus			
Yes	2 215 (14.4 %)	1 642 (11.6 %)	
No	11 987 (78.0 %)	11 254 (79.4 %)	
Undisclosed	1 003 (6.5 %)	1 147 (8.1 %)	< 0.001
Atrial Fibrillation			
Yes	2 156 (14.0 %)	2 616 (18.5 %)	
No	11 878 (77.3 %)	10 191 (71.9 %)	
Undisclosed	1 168 (7.6 %)	1 224 (8.6 %)	< 0.001
Hypertension			
Yes	6 455 (42.0 %)	6 192 (43.7 %)	
No	7 363 (47.9 %)	6 362 (44.9 %)	
Undisclosed	1 400 (9.1 %)	1 490 (10.5 %)	< 0.001
Intermittant Claudication			
Yes	672 (4.4 %)	410 (2.9 %)	
No	12 216 (79.5 %)	11 027 (77.8 %)	
Undisclosed	2 268 (14.8 %)	2 555 (18.0 %)	< 0.001
Stroke Severity (SSS)			
Very Severe (0–14 pt)	1 373 (8.9 %)	1 899 (13.4 %)	
Severe (15–29 pt)	1 294 (8.4 %)	1 426 (10.1 %)	
Moderate (30–44 pt)	2 530 (16.5 %)	2 557 (18.0 %)	
Mild (45–58 pt)	8 072 (52.5 %)	6 031 (42.5 %)	< 0.001
Smoking			
Daily	5 836 (38.1 %)	3 714 (26.2 %)	
Occasionally	267 (1.7 %)	194 (1.4 %)	
Exsmoker (more than 6 months)	3 413 (22.2 %)	1 667 (11.8 %)	
Never smoked	3 256 (21.2 %)	5 139 (36.3 %)	
Undisclosed	2 392 (15.6 %)	3 265 (23.0 %)	< 0.001
Alcohol			
14/21 drinks/week or less	11 224 (73.0 %)	10 588 (74.7 %)	
More than 14/21 drinks/week	1 532 (10.0 %)	365 (2.6 %)	
Undisclosed	2 403 (15.6 %)	3 038 (21.4 %)	< 0.001
Type of Residence			
Own residence	13 165 (85.6 %)	11 338 (78.0 %)	
Care home	680 (4.4 %)	1 380 (9.7 %)	
Other	256 (1.7 %)	268 (1.9 %)	
Undisclosed	1 092 (7.1 %)	1 008 (7.1 %)	< 0.001
Civil Status			
Cohabitant	9 670 (62.9 %)	5 070 (35.8 %)	
Lives alone	4 464 (29.0 %)	7 648 (53.9 %)	
Other	284 (1.9 %)	497 (3.5 %)	
Undisclosed	792 (5.2 %)	803 (5.7 %)	< 0.001

MRRs according to sex, followed by adjustment for patient characteristics and department and finally additionally adjusted for proportion of fulfilled quality of care criteria that each patient was deemed eligible for. We analyzed data using STATA version 9.0 (StataCorp).

Results

Table 1 shows characteristics of the 29 549 patients according to sex. Female sex was associated with higher proportions of older patients, atrial fibrillation, hypertension, severe strokes, care home residency, and more women than men were living alone. Male sex was associated with higher proportions of diabetes, myocardial infarction, former strokes, intermittant claudication, high alcohol intake, and daily smoking. We found no statistical significant differences in the distribution of the Charlson comorbidity index score between women and men.

Fulfillment of Quality of Care Criteria

Table 2 displays, according to sex and stratified by age, the proportions of patients which fulfilled the quality of care criteria. The varying number of patients included in the analysis of the specific criteria reflect that a varying proportion of the patients was eligible to the individual criteria, eg, in 2196 female patients aged 65 years or younger platelet inhibitor therapy was considered to be indicated as the patients had an ischemic or unspecified stroke and no contraindications for platelet inhibitory therapy, and of these, 1657 received the treatment within 2 days after hospitalization (75.5%). There were no major differences in the proportion of men and women deemed ineligible or with missing data for the specific quality of care criteria. In general, the differences were less than 1% for each of the indicators (data not shown). The proportion of eligible patients who fulfilled the quality of care criteria was slightly lower for women compared with men for most of the criteria (ie, the RRs ranged from 0.84 [95% confidence interval (CI): 0.74 to 0.96] to 1.01 [95% CI:0.96 to 1.06]). The largest difference was found for oral anticoagulant therapy. However, the RR remained above 0.90 for all quality of care criteria, except for oral anticoagulant therapy among patients aged ≤65 years (RR=0.84, 95% CI:0.69 to 1.03) and >80 years (RR=0.84, 95% CI:0.74 to 0.96).

The modest differences in quality of care remained when we compared the proportion of fulfilled quality of care criteria that each patient was deemed eligible for between women and men. The largest difference was found among patients aged between >65 and ≤80 years where the RR of fulfilling 100% of the criteria was 0.90 (95% CI:0.85 to 0.96) when comparing women with men. For patients ≤65 years and >80 years the corresponding RRs were 0.99 (0.92 to 1.06) and 0.94 (0.86 to 1.02), respectively.

30- and 90-Day Cumulative Mortality

The overall cumulative 30- and 90-day mortality was 12.8% and 17.4% for women and 9.7% and 12.9% for men, respectively. The corresponding overall crude MRRs were 1.34 (95% CI:1.26 to 1.44) after 30 days and 1.38 (95% CI:1.30 to 1.46) after 90 days. As expected, we found a reduction of the MRRs after adjustment for patient characteristics, including sociodemographic and clinical character-

Table 2. Fulfillment of Quality of Care Criteria According to Sex and Stratified by Age

Fulfillment of Quality of Care Criteria	Age	Male (%) (n=15 372)	Female (%) (n=14 177)	RR (95% CI)
Treatment/rehabilitation in stroke unit	≤65	4 233/5 466 (77.4 %)	2 343/3 064 (76.5 %)	0.99 (0.96–1.01)
	>65–80	5 173/6 686 (77.4 %)	4 299/5 690 (75.6 %)	0.98 (0.96–1.00)
	>80	2 328/3 112 (74.8 %)	3 980/5 320 (74.8 %)	1.00 (0.97–1.03)
Antiplatelet therapy	≤65	3 062/3 945 (77.6 %)	1 657/2 196 (75.5 %)	0.97 (0.94–1.00)
	>65–80	3 207/4 243 (75.6 %)	2 481/3 473 (71.4 %)	0.95 (0.92–0.97)
	>80	1 182/1 629 (72.6 %)	1 738/2 530 (68.7 %)	0.95 (0.91–0.99)
Oral anticoagulant therapy	≤65	148/214 (69.2 %)	51/87 (58.6 %)	0.84 (0.69–1.03)
	>65–80	398/647 (61.5 %)	338/579 (58.4 %)	0.95 (0.87–1.04)
	>80	210/431 (48.7 %)	316/769 (41.1 %)	0.84 (0.74–0.96)
CT/MRI scan	≤65	4 432/ 5 296 (83.7 %)	2 463/ 2 958 (83.2%)	0.99 (0.98–1.01)
	>65–80	5 157/ 6 474 (79.7 %)	4 364/ 5 513 (79.2 %)	0.99 (0.98–1.01)
	>80	2 347/ 2 992 (78.4 %)	3 954/ 5 075 (77.9 %)	0.99 (0.97–1.02)
Assessment by a physiotherapist	≤65	2 119/ 4 181 (50.7 %)	1 118/ 2 270 (49.3 %)	0.97 (0.92–1.02)
	>65–80	2809/ 5 399 (52.0 %)	2 215/ 4 589 (48.3 %)	0.93 (0.89–0.97)
	>80	1 231/ 2 558 (48.1 %)	1 980/ 4 280 (46.3 %)	0.96 (0.91–1.01)
Assessment by an occupational therapist	≤65	1 881/ 4 215 (44.6 %)	1 029/ 2 298 (44.8 %)	1.00 (0.95–1.06)
	>65–80	2 446/ 5 371 (45.5 %)	1 955/ 4 594 (42.6 %)	0.93 (0.89–0.98)
	>80	1 084/ 2 504 (43.3 %)	1 754/ 4 205 (41.7 %)	0.96 (0.91–1.02)
Nutritional risk evaluation	≤65	2 040/ 3 771 (54.1 %)	1 123/ 2 053 (54.7 %)	1.01 (0.96–1.06)
	>65–80	2 375/ 4 678 (50.8 %)	1 892/ 3 953 (47.9 %)	0.94 (0.90–0.98)
	>80	926/ 2 089 (44.3 %)	1 506/ 3 604 (41.8 %)	0.94 (0.88–1.00)

The varying No. of patients in the different indicator groups in relation to the total amount of patients is attributable to the fact that not all patients were deemed relevant for the individual indicator groups by hospital staff, ie, only 87 female patients≤65 were relevant for anticoagulant therapy because they had both atrial fibrillation and ischemic stroke.

istics. The adjusted MRRs were 0.79 (95% CI: 0.73 to 0.86) after 30 days and 0.81 (95% CI: 0.75 to 0.87) after 90 days. Further adjustment for differences in the proportion of fulfilled quality of care criteria had only a marginal impact on the adjusted MRRs (ie, the fully adjusted MRRs were 0.79 (95% CI 0.72 to 0.86) for 30 days and 0.81 (95% CI 0.75 to 0.87) at 90 days). Stratifying the analyses according to age did not change this pattern (Table 3). The survival advantage of female patients was also present when stratifying for age, in particular in the oldest age group for 30 day mortality (Table 3).

Discussion

In this large nationwide follow-up study, we observed no substantial sex-related differences in the quality of acute hospital care among patients with stroke when stratifying for age. Furthermore, short-term mortality appeared to be lower among women compared with men in particularly in the oldest age groups. Sex-related differences in mortality appeared not to be explained by differences in acute hospital care.

Strengths and Limitations

The main strength of our study is its prospective population-based design with complete long-term follow-up and consequently low risk of selection and information bias. Also, our analyses were based on a large cohort, with detailed data on a range of specific processes of care and only patients without contraindications for the specific processes of care were included in the analyses. Furthermore, while examining

Table 3. Crude and Adjusted Mortality Rate Ratios During 30 and 90 Days, According to Sex and Stratified for Age

		30-Day Mortality			
Age (Years)	Sex	Proportion of Patients Who Died, n (%)	Unadjusted MRR (95% CI)	Adjusted MRR[1] (95% CI)	Fully Adjusted MRR[2] (95% CI)
≤65	Male	280/5217 (5.1)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Female	171/2912 (5.5)	1.09 (0.90–1.32)	0.90 (0.71–1.14)	0.91 (0.72–1.16)
>65–80	Male	618/6123 (9.2)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Female	592/5141 (10.3)	1.13 (1.01–1.27)	0.87 (0.76–1.00)	0.86 (0.75–0.98)
>80	Male	590/2544 (18.8)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	Female	1057/4304 (19.7)	1.05 (0.95–1.16)	0.72 (0.63–0.82)	0.71 (0.63–0.81)

1: Adjusted for patient characteristics (age, civil status, type of residence, stroke severity, atrial fibrillation, hypertension, diabetes, intermittant claudication, Charlson comorbidity index score, smoking, and alcohol intake) and hospital department.

2: Adjusted for patient characteristics, hospital department, and percentage of fulfilled quality of care criteria.

mortality, we reduced confounding by adjusting for a wide range of prognostic factors.

However the use of data collected in a nonstandardized setting during routine clinical work is a limitation, potentially affecting accuracy of collected data. At the same time, participation in DNIP is mandatory for all departments treating patients with acute stroke in Denmark, and extensive efforts are made to ensure the validity of DNIP.[12] In particular, a yearly structured audit is conducted nationally, regionally, and locally, which includes validation of the completeness of patient registration against hospital discharge registries. The fact that the eligibility for the specific processes of care was determined by the staff might be a cause for concern as health professionals' could prioritize differently. However, we found no differences in the proportion of women and men considered eligible for care.

Although we adjusted for a wide range of prognostic factors, we cannot entirely exclude the possibility that our results may still be influenced by residual confounding attributable to the use of crude variables (eg, data on levels of hypertension were not available) or unaccounted confounding from factors not included in the analyses (eg, mental function or diet). The prevalence of patients with missing data on the prognostic factors ranged between 5% and 30% for the variables considered. Although missing data should always be a reason for concern, we have no reason to believe that this had any substantial influence on our findings which remained virtually unchanged whether or not patients with missing data were included in the analyses.

We used mortality as the clinical outcome. Despite its obvious importance, mortality is certainly not the only outcome relevant for patients with stroke. Examination of the possible effect of sex-related differences in quality of care on other clinical outcomes (eg, functional level after discharge) is also of major interest. Unfortunately such data were not available in our study population. Because we only found minor sex-related differences in acute hospital care after stratifying for age, it seems less likely that the differences in quality of care could explain major sex-related differences in other outcomes. However, caution is needed before extrapolating our findings to functional level and other outcomes, which may be more sensitive outcome measures than mortality.

Comparison With Other Studies

Our findings regarding quality of care are in accordance with those observed in 2005 by Kapral et al[7] in a study on 3323 patients in Canada. Among other things, this study found that there were no sex differences in the use of neuroimaging or antithrombotic therapy, and that after adjustment for age, women were as likely as men to receive care on an acute stroke unit. In our study, we also found no sex differences in the use of neuroimaging, admission to a specialized stroke unit, or antiplatelet therapy. However, our findings regarding quality of care differ from that of other studies, including three studies on patients with stroke and patients with other cardiovascular diseases including patients with coronary heart disease and congestive heart failure.[2,3,5,6,25] In a large German study, Foerch et al found sex disparities in acute stroke management in terms of early hospital admission and thrombolytic treatment. This disparity only appeared among elderly stroke patients (patients above 74 years), and no imbalances were observed in the younger patients. Early hospital admission was defined as admission within the critical first 3 hours after symptom onset. Although, in our study, early admission to a specialized stroke unit was defined as admission no later than the second day of hospitalization, we found no differences between sexes in early hospital admission and only minor differences in antiplatelet therapy or oral anticoagulant therapy irrespective of age. In another prospective joint European study on 4499 patients by Di Carlo et al, found that brain imaging and other diagnostic tools were less frequently used among women, as only 77.1% of women received brain imaging compared with 87.7% of men. However, in our study we found no differences in the use of CT/MRI scans between sexes after stratifying for age.

The lower mortality among women in our study confirms findings from other studies on patients with stroke, including a previous study based on data from DNIP.[26,27] The factors possibly underlying an improved survival among women could in theory include a more favorable prognostic patient profile (eg, less comorbidity), a more health-minded lifestyle (eg, less smoking, smaller alcohol intake, healthier diet, and more physical activity), better quality of care (including acute care, rehabilitation, and secondary prevention), or real physiological advantages compared with men. Our findings lend support to the hypothesis that women may have a physiological advantage when it comes to surviving a stroke as the

Table 3. Continued

90-Day Mortality			
Proportion of Patients Who Died, n (%)	Unadjusted MRR (95% CI)	Adjusted MRR[1] (95% CI)	Fully Adjusted MRR[2] (95% CI)
346/5151 (6.3)	1.00 (reference)	1.00 (reference)	1.00 (reference)
205/2878 (6.6)	1.06 (0.89–1.26)	0.89 (0.72–1.10)	0.90 (0.73–1.11)
834/5907 (12.4)	1.00 (reference)	1.00 (reference)	1.00 (reference)
782/4951 (13.6)	1.11 (1.01–1.22)	0.85 (0.76–0.96)	0.85 (0.75–0.95)
801/2333 (25.6)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1473/3888 (27.4)	1.08 (0.99–1.18)	0.77 (0.70–0.86)	0.77 (0.69–0.86)

better survival of women remained after taking differences in the prognostic profile, lifestyle, and quality of early care into account. Female sex hormones, in particular progesterone, are obvious candidates in the search for a physiological mechanism underlying the female survival advantage and a large and growing body of evidence, including a recently published pilot clinical trial, indeed indicates that progesterone exerts neuroprotective effects on the central nervous system.[28] The neuroprotective effects appear to include protection of the blood-brain barrier, reduction in the development of cerebral edema, downregulation of the inflammatory cascade, and limitation of cellular necrosis and apoptosis.[28]

A central aspect in the struggle against sexism is to get a clearer picture of the extent and consequences of any sex-related differential treatment. In this context it is important to be aware that in some situations there could be sound ethical and clinical reasons for treating female patients different than male patients. Thus it is well known that female stroke patients generally are older than male stroke patients and therefore form a larger part of the oldest stroke population. Previous studies indicate that age-related differences in level of care exists among patients with stroke,[9–11] and age therefore appears to be an important confounder when comparing sexes, which should always be accounted for when comparing performance measures in stroke populations. It is essential that studies of sex-related differences take these aspects into account, to avoid overestimating or misinterpreting the observed differences thus hindering the effort of effective elimination of true sexism.

In conclusion, we found only minor sex-related differences in acute hospital care among patients with stroke in Denmark when stratifying for age. The largest sex-related differences were found for early anticoagulant therapy; however, the differences were not substantial. Quality of early care did not appear to explain the observed sex-related differences in mortality.

Sources of Funding

This work was supported by grants from the Foundation for Research in Neurology and The Aarhus University Research Foundation.

Disclosures

None.

References

1. American Heart Association. American Stroke Association. Heart Disease and Stroke Statistics 2008 Update. 2008.
2. Foerch C, Misselwitz B, Humpich M, Steinmetz H, Neumann-Haefelin T, Sitzer M. Sex disparity in the access of elderly patients to acute stroke care. *Stroke*. 2007;38:2123–2126.
3. Di CA, Lamassa M, Baldereschi M, Pracucci G, Basile AM, Wolfe CD, Giroud M, Rudd A, Ghetti A, Inzitari D. Sex differences in the clinical presentation, resource use, and 3-month outcome of acute stroke in Europe: data from a multicenter multinational hospital-based registry. *Stroke*. 2003;34:1114–1119.
4. Gargano JW, Wehner S, Reeves M. Sex differences in acute stroke care in a statewide stroke registry. *Stroke*. 2008;39:24–29.
5. Holroyd-Leduc JM, Kapral MK, Austin PC, Tu JV. Sex differences and similarities in the management and outcome of stroke patients. *Stroke*. 2000;31:1833–1837.
6. Jani SM, Montoye C, Mehta R, Riba AL, DeFranco AC, Parrish R, Skorcz S, Baker PL, Faul J, Chen B, Roychoudhury C, Elma MA, Mitchell KR, Eagle KA. Sex differences in the application of evidence-based therapies for the treatment of acute myocardial infarction: the American College of Cardiology's Guidelines Applied in Practice projects in Michigan. *Arch Intern Med*. 2006;166:1164–1170.
7. Kapral MK, Fang J, Hill MD, Silver F, Richards J, Jaigobin C, Cheung AM. Sex differences in stroke care and outcomes: results from the Registry of the Canadian Stroke Network. *Stroke*. 2005;36:809–814.
8. Rundek T. Do women have worse outcome after stroke caused by intracranial arterial stenosis? *Stroke*. 2007;38:2025–2027.
9. Bhalla A, Grieve R, Tilling K, Rudd AG, Wolfe CD. Older stroke patients in Europe: stroke care and determinants of outcome. *Age Ageing*. 2004; 33:618–624.
10. Di CA, Lamassa M, Pracucci G, Basile AM, Trefoloni G, Vanni P, Wolfe CD, Tilling K, Ebrahim S, Inzitari D. Stroke in the very old: clinical presentation and determinants of 3-month functional outcome: A European perspective. European BIOMED Study of Stroke Care Group. *Stroke*. 1999;30:2313–2319.
11. Palnum KD, Petersen P, Sorensen HT, Ingeman A, Mainz J, Bartels P, Johnsen SP. Older patients with acute stroke in Denmark: quality of care and short-term mortality. A nationwide follow-up study. *Age Ageing*. 2008;37:90–95.
12. Mainz J, Krog BR, Bjornshave B, Bartels P. Nationwide continuous quality improvement using clinical indicators: the Danish National Indicator Project. *Int J Qual Health Care* 2004;16 Suppl 1:i45–i50.
13. The World Health Organization MONICA Project (monitoring trends and determinants in cardiovascular disease): a major international collaboration. WHO MONICA Project Principal Investigators. *J Clin Epidemiol* 1988;41:105–114.
14. Referenceprogram for Behandling af Patienter med Apopleksi. *www.sst.dk/publ/Publ2006/CEMTV/SfR/Apopl_refprg.pdf*. 2006.
15. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71–86.
16. Chen ZM, Sandercock P, Pan HC, Counsell C, Collins R, Liu LS, Xie JX, Warlow C, Peto R. Indications for early aspirin use in acute ischemic stroke: A combined analysis of 40 000 randomized patients from the chinese acute stroke trial and the international stroke trial. On behalf of the CAST and IST collaborative groups. *Stroke*. 2000;31:1240–1249.
17. Gubitz G, Sandercock P, Counsell C. Antiplatelet therapy for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2000;CD000029.
18. Kondrup J, Allison SP, Elia M, Vellas B, Plauth M. ESPEN guidelines for nutrition screening 2002. *Clin Nutr*. 2003;22:415–421.
19. Charlson ME, Pompei P, Ales KL, Mackenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373–383.
20. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45:613–619.
21. Goldstein LB, Samsa GP, Matchar DB, Horner RD. Charlson Index comorbidity adjustment for ischemic stroke outcome studies. *Stroke*. 2004;35:1941–1945.
22. Multicenter trial of hemodilution in ischemic stroke–background and study protocol. Scandinavian Stroke Study Group. *Stroke*. 1985;16:885–890.
23. Lindenstrøm L, Boysen G, Christiansen LW, á Rogvi-Hansen B, Nielsen PW. Reliability of Scandinavian Neurological Stroke Scale. *Cerebrovasc Dis*. 1991;1:103–107.
24. Pedersen CB, Gotzsche H, Moller JO, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. *Dan Med Bull*. 2006;53:441–449.
25. Rathore SS, Foody JM, Wang Y, Herrin J, Masoudi FA, Havranek EP, Ordin DL, Krumholz HM. Sex, quality of care, and outcomes of elderly patients hospitalized with heart failure: findings from the National Heart Failure Project. *Am Heart J*. 2005;149:121–128.
26. Olsen TS, Dehlendorff C, Andersen KK. Sex-related time-dependent variations in post-stroke survival–evidence of a female stroke survival advantage. *Neuroepidemiology*. 2007;29:218–225.
27. van SA, Reitsma JB, Limburg M, van den Bos GA, de Haan RJ. Impact of stroke type on survival and functional health. *Cerebrovasc Dis*. 2001;12: 27–33.
28. Stein DG, Wright DW, Kellermann AL. Does progesterone have neuroprotective properties? *Ann Emerg Med*. 2008;51:164–172.

Title page:

Medical Prophylaxis Following Hospitalization with Ischemic Stroke: Age- and Sex-Related Differences and Relation to Mortality

Kaare Haurvig Palnum[a], Frank Mehnert[a], Grethe Andersen[b], Annette Ingeman[c], Birgitte Randrup Krog[c], Paul Daniel Bartels[c], Søren Paaske Johnsen[a]

[a]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark, [b] Department of Neurology, Aarhus University Hospital, Kommunehospitalet, Aarhus, Denmark, [c] The Coordinating Secretariat (NIP), County of Aarhus, Aarhus, Denmark.

Correspondence to Kaare H Palnum, Department of Clinical Epidemiology, Aarhus University Hospital, Ole Worms Allé 43-45, 8200 Aarhus N, Denmark. kdp@dce.au.dk, Tel: +45 89 42 33 64 Fax: +45 89 42 48 01.

Key Words*:* ■ Medical prophylaxis ■ Ischemic stroke ■ Age ■ Sex

Abstract

Background: The extent and implications of age- and sex-related differences in prophylaxis following ischemic stroke are unknown. We examined the use of medical prophylaxis in stroke patients following hospital discharge in Denmark, analyzed the differences across age and sex groups, and determined the relationship of drug use and 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% CI (confidence intervals): 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. Drug perseverance ranged from 66.1% to 91.9% for different drugs 12–18 months after discharge, with the lowest perseverance found among patients >80 years. Lower prophylaxis contributed to the increased mortality rate ratios in elderly patients.

Conclusions: Continuous efforts are warranted to ensure implementation of evidence-based secondary prophylaxis among elderly patients with ischemic stroke.

Introduction

Although stroke is an event that is independent 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 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 post-discharge stroke care 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 the 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, had an impact on mortality.

Methods

Setting and design

This population-based follow-up study was conducted using data from the entire Danish population (approximately 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 30th, 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 (≥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 that last more than 24 hours or until death with no apparent non-vascular cause[19]). We excluded 4870 patients who died in the hospital or within 30 days after hospital discharge. We also excluded 2548 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.

Medical prophylaxis

Data for prescriptions filled after discharge was obtained by linkage with the Medical Register of the Danish Medicines 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 acetyl salicylic 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 dipyridamol. Drug use was assessed for two time windows: 0–6 months 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, never), and alcohol intake (≤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 scan, early assessment by a physiotherapist and by an occupational therapist, and assessment of nutritional risk. 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 socioeconomic status (SES) the year prior to hospital admission was obtained from the Integrated Database for Labor Market Research (IDA). SES 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 preadmission modified Rankin score (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 Copenhagen and Aarhus areas (n=6501).

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 months and 12–18 months after hospital discharge. We defined perseverance to medical prophylaxic 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 ≤65 years as a reference. Comparisons of oral anticoagulant therapy 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 the two follow-up periods, 30 days–6 months and 12–18 months). Follow-up started on day 30 after hospital discharge and ended on the date of death, emigration, or after 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, the Copenhagen and Aarhus County areas. In these analyses, we also adjusted for preadmission modified Rankin score 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 1 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 months and 12–18 months after discharge. In contrast, we identified no overall systematic sex-related differences in prophylaxis after hospital discharge. However, between 0–6 months, women ≤65 years were less likely to receive ACE inhibitors/ATII antagonists (adjusted OR 0.74, 95%CI: 0.67–0.83), but more likely to receive thiazides (adjusted OR 1.13, 95%CI: 1.01–1.28) compared with men of the same age. The more widespread use of thiazides among women was seen in all age groups in both time windows.

Perseverance with prophylaxis 12–18 months after discharge ranged from 66.1% (thiazide therapy among males ≤65 years) to 91.9% (antiplatelet therapy among males >65 to 80 years). There were no substantial differences in perseverance across age groups for most drug groups. However, for anticoagulant therapy, ACE inhibitors/ATII antagonists, statins, and

combination therapy, a decrease in drug perseverance was observed with increasing age. No systematic sex differences in drug perseverance 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 the exact same results as the original analysis, indicating that differences in preadmission modified Rankin scores 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 mortality rate ratios (MRRs) for 30 days-6 months and 12–18 months are presented in Table 3. The range for cumulative mortality was 1.8%–12.2% for the 30-day–6 month period and 1.4%–10.7% for the 12–18 month period, respectively, for men in the three age groups. The corresponding mortality for women ranged from 1.4%–13.3% within the first 6 months and from 1.3%–9.3% for the 12–18 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 12–18 month 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 lower drug perseverance. In contrast, we found no indication of any sex-related differences in prophylaxis. The age-related differences in the use of secondary prophylaxis appeared to contribute to 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 for 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. Furthermore, 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. Further, in our drug perseverance analysis, we used a rather conservative approach in which all included patients 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 true perseverance with 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 is 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. examined in-hospital use of statins among 1743 Austrian patients admitted with ischemic stroke between 1998–2001 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) [29]. Ovbiagele et al. found similar patterns for overall statin use during hospitalization in a study of 2894 patients with ischemic stroke admitted between 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 [30]. In the present study, we

found that between 28% and 66% of patients received statin treatment up to 6 months after discharge. Like Lalouschek et al., we found that elderly people were less likely to receive statins.

Underuse of oral anticoagulant therapy among ischemic stroke patients has been found consistently, including a recent study [31]. We reported previously that fewer than 70% percent of eligible Danish ischemic stroke patients receive oral anticoagulant therapy in the early phase after stroke: this percentage was as low as 44% for patients over 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. Furthermore, 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 Hypertension in the Very Elderly Trial (HYVET) were first published in 2008 [32]. However, clinical guidelines have consistently recommended use of prophylaxis independent of patient age, and thorough efforts were made in the present study to minimize the impact of any age-related differences in prognostic factors (including stroke severity, comorbidity, functional level etc.) that could explain the substantial age-related differences in prophylaxis.

Other studies have investigated potential sex-related differences in the treatment of stroke patients [6-9;13;33]. However, these studies mainly investigated in-hospital treatment and

quality of care. In agreement with the studies that found no sex-related differences in stroke treament[13;33], we found no systematic differences between men and women in use of medical prophylaxis 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. Drug perseverance also appeared to be lower among elderly patients. These age-related differences in the use of secondary prophylaxis contributed to the higher mortality that was observed among 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.

Funding Sources

Supported by grants from the Aarhus University Research Foundation.

Disclosures

None

Acknowledgements

None

Reference List

1. American Heart Association. American Stroke Association. Heart Disease and Stroke Statistics 2009 Update. 2009.

   Ref Type: Report

2. Olsen TS, Dehlendorff C, Andersen KK: Sex-related time-dependent variations in post-stroke survival--evidence of a female stroke survival advantage. Neuroepidemiology. 2007;29:218-225.

3. Bhalla A, Grieve R, Tilling K, Rudd AG, Wolfe CD: Older stroke patients in Europe: stroke care and determinants of outcome. Age Ageing. 2004;33:618-624.

4. Di CA, Lamassa M, Pracucci G et al: Stroke in the very old : clinical presentation and determinants of 3-month functional outcome: A European perspective. European BIOMED Study of Stroke Care Group. Stroke. 1999;30:2313-2319.

5. Palnum KD, Petersen P, Sorensen HT et al: Older patients with acute stroke in Denmark: quality of care and short-term mortality. A nationwide follow-up study. Age Ageing. 2008;37:90-95.

6. Foerch C, Misselwitz B, Humpich M, Steinmetz H, Neumann-Haefelin T, Sitzer M: Sex disparity in the access of elderly patients to acute stroke care. Stroke. 2007;38:2123-2126.

7. Di CA, Lamassa M, Baldereschi M et al: Sex differences in the clinical presentation, resource use, and 3-month outcome of acute stroke in Europe: data from a multicenter multinational hospital-based registry. Stroke. 2003;34:1114-1119.

8. Gargano JW, Wehner S, Reeves M: Sex differences in acute stroke care in a statewide stroke registry. Stroke. 2008;39:24-29.

9. Holroyd-Leduc JM, Kapral MK, Austin PC, Tu JV: Sex differences and similarities in the management and outcome of stroke patients. Stroke. 2000;31:1833-1837.

10. Warlow C: Stroke
a practical guide to management. Oxford, Blackwell Science, 2001.

11. Stevens A: Health care needs assessment
the epidemiologically based needs assessment reviews. Oxford, Radcliffe, 2004.

12. Kwakkel G, Wagenaar RC, Kollen BJ, Lankhorst GJ: Predicting disability in stroke--a critical review of the literature. Age Ageing. 1996;25:479-489.

13. Palnum KD, Andersen G, Ingeman A, Krog BR, Bartels P, Johnsen SP: Sex-Related Differences in Quality of Care and Short-Term Mortality Among Patients With Acute Stroke in Denmark. A Nationwide Follow-Up Study. Stroke. 2009.

14. Adams HP, Jr., del ZG, Alberts MJ et al: Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular

Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Stroke. 2007;38:1655-1711.

15. Adams RJ, Albers G, Alberts MJ et al: Update to the AHA/ASA recommendations for the prevention of stroke in patients with stroke and transient ischemic attack. Stroke. 2008;39:1647-1652.

16. ESO Guidelines for Stroke Management - January 2009. http://www.eso-stroke.org/recommendations.php?cid=9&sid=1. 2009.
Ref Type: Generic

17. Pedersen CB, Gotzsche H, Moller JO, Mortensen PB: The Danish Civil Registration System. A cohort of eight million persons. Dan Med Bull. 2006;53:441-449.

18. Mainz J, Krog BR, Bjornshave B, Bartels P: Nationwide continuous quality improvement using clinical indicators: the Danish National Indicator Project. Int J Qual Health Care. 2004;16 Suppl 1:i45-i50.

19. The World Health Organization MONICA Project (monitoring trends and determinants in cardiovascular disease): a major international collaboration. WHO MONICA Project Principal Investigators. J Clin Epidemiol. 1988;41:105-114.

20. Multicenter trial of hemodilution in ischemic stroke--background and study protocol. Scandinavian Stroke Study Group. Stroke. 1985;16:885-890.

21. Lindenstrøm L, Boysen G, Christiansen LW, á Rogvi-Hansen B, Nielsen PW: Reliability of Scandinavian Neurological Stroke Scale. Cerebrovasc Dis. 1991;1:103-107.

22. Ingeman A, Pedersen L, Hundborg HH et al: Quality of care and mortality among patients with stroke: a nationwide follow-up study. Med Care. 2008;46:63-69.

23. Andersen TF, Madsen M, Jorgensen J, Mellemkjoer L, Olsen JH: The Danish National Hospital Register. A valuable source of data for modern health sciences. Dan Med Bull. 1999;46:263-268.

24. Deyo RA, Cherkin DC, Ciol MA: Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol. 1992;45:613-619.

25. Goldstein LB, Samsa GP, Matchar DB, Horner RD: Charlson Index comorbidity adjustment for ischemic stroke outcome studies. Stroke. 2004;35:1941-1945.

26. Charlson ME, Pompei P, Ales KL, Mackenzie CR: A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40:373-383.

27. Statistics Denmark: Statistics Denmark's Classification of Occupational Skills. Copenhagen, 1996.

28. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van GJ: Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 1988;19:604-607.

29. Lalouschek W, Lang W, Greisenegger S, Mullner M: Determination of lipid profiles and use of statins in patients with ischemic stroke or transient ischemic attack. Stroke. 2003;34:105-110.

30. Ovbiagele B, Saver JL, Bang H et al: Statin treatment and adherence to national cholesterol guidelines after ischemic stroke. Neurology. 2006;66:1164-1170.

31. Gladstone DJ, Bui E, Fang J et al: Potentially preventable strokes in high-risk patients with atrial fibrillation who are not adequately anticoagulated. Stroke. 2009;40:235-240.

32. Beckett NS, Peters R, Fletcher AE et al: Treatment of hypertension in patients 80 years of age or older. N Engl J Med. 2008;358:1887-1898.

33. Kapral MK, Fang J, Hill MD et al: Sex differences in stroke care and outcomes: results from the Registry of the Canadian Stroke Network. Stroke. 2005;36:809-814.

Table 1. Characteristics of 28 634 Patients Admitted with Ischemic Stroke in Denmark, 2003-2006, Stratified by Age

	≤65 n=9019	**> 65–80** n=12 173	**>80** n=7442	***P*-value, chi-square**
Sex				
Male	5751 (63.8%)	6643 (54.6%)	2785 (37.4%)	
Female	3268 (36.2%)	5530 (45.4%)	4657 (62.6%)	*P*=0.0001
Comorbidity				
Charlson Index				
None (0 pt)	5194 (57.6%)	5160 (42.4%)	2943 (39.5%)	
Low (1–2 pt)	2906 (32.2%)	4857 (39.9%)	3167 (42.6%)	
High (>2 pt)	919 (10.2%)	2156 (17.7%)	1332 (17.9%)	*P*=0.0001
Diabetes mellitus				
Yes	1205 (13.4%)	1782 (14.6%)	811 (10.9%)	
No	7322 (81.2%)	9654 (79.3%)	6097 (91.9%)	
Undisclosed	426 (4.7%)	644 (5.3%)	477 (6.4%)	*P*=0.0001
Atrial fibrillation				
Yes	477 (5.3%)	1785 (14.7%)	1915 (25.7%)	
No	7980 (88.5%)	9528 (78.3%)	4928 (66.2%)	
Undisclosed	490 (4.7%)	760 (6.2%)	544 (7.3%)	*P*=0.0001
Myocardial infarction				
Yes	569 (6.3%)	1334 (11.0%)	725 (9.7%)	
No	7906 (87.7%)	9926 (81.5%)	5975 (80.3%)	
Undisclosed	475 (5.3%)	817 (6.7%)	679 (9.1%)	*P*=0.0001
Hypertension				
Yes	3570 (39.6%)	5825 (47.9%)	3255 (43.7%)	
No	4847 (53.7%)	5384 (44.2%)	3403 (45.7%)	
Undisclosed	538 (6.0%)	879 (7.2%)	729 (9.8%)	*P*=0.0001
Previous stroke				
Yes	1563 (17.3%)	2878 (23.6%)	1738 (23.4%)	
No	6958 (77.1%)	8521 (70.0%)	5084 (68.3%)	
Undisclosed	425 (4.7)	685 (5.6%)	566 (7.6%)	*P*=0.0001
Intermittent claudication				
Yes	270 (3.0%)	584 (4.8%)	236 (3.2%)	
No	7853 (87.1%)	9939 (81.6%)	5837 (78.4%)	
Undisclosed	809 (9.0%)	1528 (12.6%)	1300 (17.5%)	*P*=0.0001
Stroke severity score (SSS)				
Very severe (0–14 pt)	344 (3.8%)	575 (4.7%)	475 (6.4%)	
Severe (15–29 pt)	480 (5.3%)	851 (7.0%)	742 (10.0%)	
Moderate (30–44 pt)	1052 (11.7%)	2077 (17.1%)	1765 (23.7%)	
Mild (45–58 pt)	5912 (65.6%)	7003 (57.5%)	3312 (44.5%)	*P*=0.0001
Smoking				
Daily	4796 (53.2%)	4188 (34.4%)	1112 (14.9%)	
Occasionally	156 (1.7%)	212 (1.7%)	97 (1.3%)	
Ex-smoker (more than 6	1204 (13.3%)	2620 (21.5%)	1401 (18.8%)	

months)				
Never smoked	1976 (21.9%)	3380 (27.8%)	2976 (40.0%)	
Undisclosed	795 (8.8%)	1635 (13.4%)	1792 (24.1%)	*P*=0.0001
Alcohol				
14/21 drinks/week or fewer	6829 (75.7%)	9665 (79.4%)	5775 (77.6%)	
More than 14/21 drinks/week	1183 (13.1%)	697 (5.7%)	112 (1.5%)	
Undisclosed	910 (10.1%)	1659 (13.6%)	1495 (20.1%)	*P*=0.0001
Residence type				
Own residence	8051 (89.3%)	10 721 (88.1%)	5886 (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%)	*P*=0.0001
Civil status				
Co-habitant	6143 (68.1%)	6746 (55.4%)	2191 (29.4%)	
Lives alone	2326 (25.8%)	4652 (38.2%)	4622 (62.1%)	
Other	118 (1.3%)	157 (1.3%)	283 (3.8%)	
Undisclosed	361 (4.00%)	500 (4.1%)	291 (3.9%)	*P*=0.0001
Percentage of fulfilled indicators				
<50%	1676 (18.6%)	2667 (21.9%)	1939 (26.1%)	
50%–99%	4206 (46.6%)	5768 (47.4%)	3573 (48.0%)	
100%	3114 (34.5%)	3697 (30.4%)	1903 (25.6%)	*P*=0.0001
Socioeconomic status				
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 (0%)	
Salaried employee, intermediate level	614 (6.8%)	18 (0.1%)	0 (0%)	
Salaried employee, basic level	1581 (17.5%)	48 (0.4%)	1 (0.0%)	
Salaried employee, other	509 (5.6%)	29 (0.2%)	0 (0%)	
Employee, not further specified	707 (7.8%)	108 (0.9%)	18 (0.2%)	
Assisting spouse	24 (0.3%)	11 (0.1%)	0 (0%)	
Unemployed	413 (4.6%)	4 (0.0%)	0 (0%)	
Disability supplement	2218 (24.6%)	307 (2.5%)	0 (0%)	
Old-age pensioners	43 (0.5%)	10 629 (87.3%)	7373 (99.1%)	
Early retirement benefits	1112 (12.3%)	695 (5.7%)	1 (0.0%)	
Other economically inactive persons	264 (2.9%)	4 (0.0%)	0 (0%)	
Other	416 (4.6%)	34 (0.3%)	1 (0.0%)	*P*=0.0001
Rankin Score*				
No symptoms	1182 (60.3%)	1246 (46.2%)	547 (29.6%)	

Light symptoms	214 (10.9%)	448 (16.6%)	315 (17.1%)	
Modest symptoms	129 (6.6%)	245 (9.1%)	242 (13.1%)	
Moderate handicap	50 (2.5%)	142 (5.3%)	189 (10.2%)	
Needs much help	32 (1.6%)	113 (4.2%)	146 (7.9%)	
Needs constant supervision	3 (0.2%)	14 (0.5%)	16 (0.9%)	
Undisclosed	262 (13.3%)	362 (13.4%)	312 (16.9%)	*P*=0.0001
Discharge residence*				
Rehabilitation ward	46 (2.3%)	86 (3.2%)	61 (3.3%)	
Own residence	1612 (82.2%)	2004 (74.4%)	1068 (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%)	*P*=0.0001

*Information only available for the Copenhagen area and Aarhus County: ≤65 n=1961, >65–80 n=2694, >80 n=1846.

Figure 1. Proportions of Patients Receiving Medical Prophylaxis after Hospital Discharge by Age and Sex

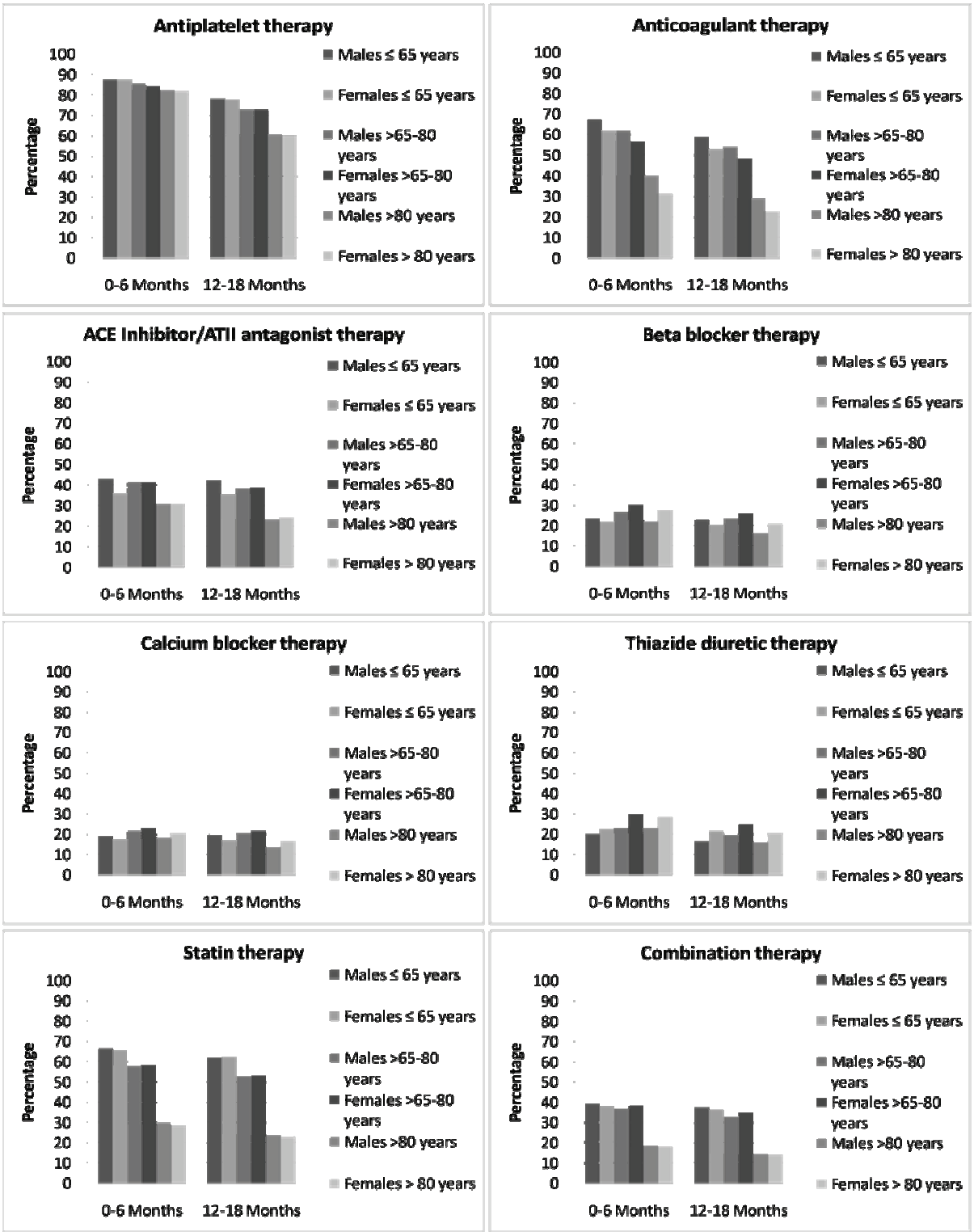


Table 2. Adjusted Odds Ratios (OR) for Medical Prophylaxis after Hospital Discharge by Age and Sex Among Patients with Ischemic Stroke

	Adjusted OR 0–6 months* (95% CI) (n=24 179)	Adjusted OR 12–18 months* (95% CI) (n=21 017)
Antiplatelets		
Males ≤65 years	1.00	1.00
Females ≤65 years	1.10 (0.95-1.29)	1.00 (0.88-1.13)
Males >65–80 years	1.01 (0.83-1.23)	1.08 (0.90-1.30)
Females >65–80 years	1.02 (0.83-1.26)	1.03 (0.85-1.26)
Males >80 years	1.07 (0.84-1.35)	1.14 (0.91-1.43)
Females >80 years	1.19 (0.94-1.49)	1.16 (0.93-1.44)
Oral anticoagulants†	*n=3537 pt*	*n=2718*
Males ≤65 years	1.00	1.00
Females ≤65 years	1.05 (0.56-1.96)	0.90 (0.51-1.59)
Males >65–80 years	0.77 (0.42-1.42)	1.07 (0.59-1.95)
Females >65–80 years	0.67 (0.36-1.24)	0.74 (0.40-1.37)
Males >80 years	0.42 (0.22-0.79)	0.46 (0.24-0.88)
Females >80 years	0.45 (0.24-0.85)	0.56 (0.29-1.06)
ACE inhibitors/ATII antagonists		
Males ≤65 years	1.00	1.00
Females ≤65 years	0.74 (0.67-0.83)	0.75 (0.68-0.84)
Males >65–80 years	0.87 (0.75-1.01)	0.88 (0.76-1.02)
Females >65–80 years	0.87 (0.75-1.02)	0.89 (0.76-1.04)
Males >80 years	0.63 (0.53-0.76)	0.57 (0.47-0.69)
Females >80 years	0.62 (0.52-0.74)	0.58 (0.49-0.70)
Beta blockers		
Males ≤65 years	1.00	1.00
Females ≤65 years	0.97 (0.86-1.10)	0.94 (0.84-1.07)
Males >65–80 years	0.88 (0.75-1.03)	0.87 (0.73-1.02)
Females >65–80 years	1.10 (0.93-1.30)	1.07 (0.90-1.27)
Males >80 years	0.61 (0.50-0.74)	0.62 (0.50-0.76)
Females >80 years	0.88 (0.73-1.06)	0.91 (0.75-1.11)
Calcium blockers		
Males ≤65 years	1.00	1.00
Females ≤65 years	0.91 (0.80-1.04)	0.85 (0.75-0.97)
Males >65–80 years	0.97 (0.82-1.15)	0.99 (0.84-1.17)
Females >65–80 years	1.03 (0.86-1.23)	1.06 (0.89-1.27)
Males >80 years	0.81 (0.66-0.99)	0.78 (0.63-0.96)
Females >80 years	0.99 (0.81-1.20)	1.02 (0.84-1.25)
Thiazide diuretics		
Males ≤65 years	1.00	1.00
Females ≤65 years	1.13 (1.01-1.28)	1.36 (1.20-1.53)
Males >65–80 years	0.98 (0.84-1.15)	1.12 (0.94-1.32)
Females >65–80 years	1.23 (1.04-1.46)	1.39 (1.17-1.67)
Males >80 years	1.06 (0.88-1.28)	1.15 (0.94-1.42)
Females >80 years	1.27 (1.06-1.53)	1.43 (1.18-1.75)

Statins		
Males ≤65 years	1.00	1.00
Females ≤65 years	1.00 (0.90-1.11)	1.02 (0.92-1.14)
Males >65–80 years	0.96 (0.83-1.10)	1.00 (0.86-1.16)
Females >65–80 years	1.23 (1.05-1.43)	1.24 (1.06-1.45)
Males >80 years	0.37 (0.31-0.44)	0.39 (0.32-0.46)
Females >80 years	0.46 (0.38-0.54)	0.47 (0.39-0.56)
Combination therapy (antiplatelet, antihypertensive,[‡] & statin)		
Males ≤65 years	1.00	1.00
Females ≤65 years	1.00 (0.90-1.11)	0.99 (0.89-1.10)
Males >65–80 years	0.93 (0.81-1.08)	0.92 (0.79-1.06)
Females >65–80 years	1.18 (1.01-1.38)	1.19 (1.02-1.40)
Males >80 years	0.45 (0.38-0.54)	0.44 (0.37-0.54)
Females >80 years	0.52 (0.43-0.62)	0.52 (0.43-0.62)

***** 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.

[†] Only includes patients with atrial fibrillation and no contraindications for anticoagulant therapy during hospital admission.

[‡] Antihypertensive: ACE inhibitor, ATII antagonist, beta blocker, calcium blocker, or thiazide diuretic.

Table 3. Cumulative Mortality Rates and Mortality Rate Ratios (MRR) 1–6 and 12–18 Months after Hospital Discharge Among Patients with Ischemic Stroke

		1–6 months				12–18 months			
Age	**Sex**	**Proportion of patients who died n (%)**	**Unadjusted MRR (95% CI) n=28 632**	**Adjusted MRR* (95% CI) n=24 179**	**Fully adjusted MRR† (95%CI) n=24 179**	**Proportion of patients who died n (%)**	**Unadjusted MRR (95% CI) n=25 532**	**Adjusted MRR* (95% CI) n=21 662**	**Fully adjusted MRR† (95%CI) n=21 662**
≤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)

*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)
†Additionally adjusted for use of antiplatelets, ACE-inhibitors/ATII antagonists, beta blockers, calcium blockers, thiazide diuretics and statins.

Effectiveness of Secondary Medical Prophylaxis Following Hospitalization with Ischemic Stroke

Kaare Haurvig Palnum[a], Frank Mehnert[a], Grethe Andersen[b], Annette Ingeman[c], Birgitte Randrup Krog[c], Paul Daniel Bartels[c], Søren Paaske Johnsen[a]

[a]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark, [b] Department of Neurology, Aarhus University Hospital, Aarhus Hospital, Aarhus, Denmark, [c] The NIP Secretariat, Aarhus, Denmark.

Correspondence to Kaare H Palnum, Department of Clinical Epidemiology, Aarhus University Hospital, Ole Worms Allé 43-45, 8200 Aarhus N, Denmark. kdp@dce.au.dk, Tel: +45 89 42 33 64 Fax: +45 89 42 48 01.

Key Words: ■ Effectiveness ■ Medical prophylaxis ■ Ischemic stroke ■ Age ■ Sex

Abstract

Background: Only sparse data exist on the effectiveness of secondary medical prophylaxis following ischemic stroke. We examined the effectiveness of prescribed secondary medical prophylaxis in Danish ischemic stroke patients following hospital discharge in a nationwide, population-based follow-up study.

Methods: Using medical databases, 28 612 patients hospitalized for ischemic stroke in 2003-2006 and surviving at least 30 days after discharge were identified and data on drug use and clinical outcome was obtained. We used regression analyses to compute adjusted mortality rate ratios (MRR) and hazard ratios (HR) of myocardial infarction and recurrent stroke according to use of secondary medical prophylaxis following hospital discharge. Risk estimates were computed both overall and stratified for age and sex.

Results: Overall, secondary prophylactic treatment with antiplatelets, oral anticoagulants, antihypertensives and statins was associated with a lower risk of death with adjusted MRRs ranging from 0.36 (95% confidence interval (CI) 0.32–0.41) to 0.85 (95%CI 0.80–0.90). Oral anticoagulant therapy in patients with atrial fibrillation was also associated with a lower risk of recurrent stroke (adjusted HR 0.58 (95%CI 0.46–0.73)) and statin therapy with lower risk of both myocardial infarction (adjusted HR 0.80 (95%CI 0.64–0.92)) and recurrent stroke (adjusted HR 0.84 (95%CI 0.77–0.91)). Less consistent associations with myocardial infarction and recurrent stroke were found for antiplatelets and antihypertensives. Effectiveness of antiplatelets and oral anticoagulants appeared to vary by age but not sex.

Conclusions: Secondary medical prophylaxis in general appears to be effective in routine clinical settings following ischemic stroke.

Introduction

The efficacy of secondary medical prophylaxis following stroke have been investigated in a number of large randomized clinical trials (RCT).[1-3] However, results on efficacy found in RCTs cannot automatically be expected to represent effectiveness in clinical settings. The external validity of RCTs is impaired if those participating are not representative of the population for whom the treatment is intended or if the treatment is not comparable to the treatment offered in everyday clinical settings. The first scenario is often the case due to strict inclusion and exclusion criteria resulting in selected patient populations, e.g., women and elderly patients have been reported to be underrepresented in cardiovascular RCTs. [4-7] The latter phenomenon occurs when patients participating in RCTs receive a different level of treatment and care than patients who do not (e.g., more intensive attention and follow-up). Such differences in care may translate into differences in outcomes. Yet only few studies have examined the effectiveness of secondary stroke prevention.[8-11]

Based on findings from RCTs, 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.[1-3]

A number of studies show an insufficient implementation of current guidelines regarding use of secondary prophylaxis in stroke patients.[12-20] Evidence of the effectiveness of secondary medical prophylaxis in patients with ischemic stroke would potentially be a strong argument for further strengthening the efforts to ensure compliance with the current clinical guidelines. We therefore examined the effectiveness of secondary medical prophylaxis following ischemic stroke in a nationwide, population-based follow-up study.

Methods

Setting and design

The study was based on data sources covering the entire Danish population (approximately 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.[21] Each record carries a unique 10-digit civil registration number that is assigned to every Danish citizen. The civil registration number is used in all Danish registries and provides unambiguous linkage between these.

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 30th, 2006 (n=36 075). DNIP is a nationwide initiative to monitor and improve the quality of care for specific diseases, including stroke.[22] This is accomplished by monitoring fulfilment 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 (≥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 that last more than 24 hours or until death with no apparent non-vascular cause[23]). We excluded 4870 patients who died in the hospital or within 30 days after hospital discharge. We also excluded 2548 patients with hemorrhagic stroke and 45 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 28 612 patients were available for further analysis.

Medical prophylaxis

Data for prescriptions filled after discharge was obtained by linkage with the Medical Register of the Danish Medicines 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 acetyl salicylic 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 dipyridamol.

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[24, 25]), history of stroke and myocardial infarction (AMI), previous and/or current atrial fibrillation, hypertension, diabetes mellitus or intermittent claudication, smoking habits (smoker, ex-smoker, never), and alcohol intake (≤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[26], was

obtained from the DNIP and included data on fulfilment of seven quality of care criteria: early admission to a specialized stroke unit, early administration of antiplatelet or anticoagulant therapy, early examination with CT/MRI scan, early assessment by a physiotherapist and by an occupational therapist, and assessment of nutritional risk. 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.[27] The Charlson comorbidity index covers 19 major disease categories and has been reported to be useful for patients with stroke.[28-30] We defined three levels of comorbidity: 0 comorbidities ("low"), 1–2 comorbidities ("moderate"), and >2 comorbidities ("high"). Former stroke, AMI, 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 socioeconomic status (SES) the year prior to hospital admission was obtained from the Integrated Database for Labor Market Research (IDA). SES 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.[31]

End points

The end-points included death and hospitalisation with AMI and recurrent stroke. We obtained information on mortality after discharge up to 31 December 2007 from the Civil Registration System, whereas information on hospitalisations with AMI and recurrent stroke during the same time period were obtained from the National Registry of Patients and DNIP, respectively.[27]

Statistical Analysis

We first assessed the cumulative incidence of death, AMI and recurrent stroke. Death was considered a competing risk in relation to AMI and recurrent stroke. Patients were followed from the date of discharge until date of outcome (AMI or recurrent stroke), date of death or 31 December 2007, whichever came first for each patient.

Second we used Cox Proportional Hazards Regression analysis (with the Efron approximation to handle tied survival times) to compute drug specific mortality rate ratios (MRR) and Hazard Ratios (HR) for AMI and recurrent stroke according to use of secondary medical prophylaxis with no treatment as reference. Drug use was included as time-dependent variables with dates of filling for each prescription as start date and 90 day duration for each prescription. Thus, prescriptions filled within a 90 day period before outcome dates was regarded as current use of the drug in question. For death, follow-up started on day 30 after hospital discharge and ended on date of death or on 31 December 2007. For AMI and recurrent stroke, follow-up started on hospital discharge and ended on date of AMI/ recurrent stroke, date of death or 31 December 2007, whichever came first. Multiple imputation was used to impute missing values for former stroke, former AMI, diabetes, atrial fibrillation, hypertension, intermittent claudication, Scandinavian Stroke Scale Score, smoking, alcohol consumption, type of residence at hospitalisation, civil status and percentage of fulfilled indicators during hospitalisation. We generated five imputed data sets, and the MRRs/HRs were then averaged across the five imputations, correcting for between- and within-imputation variation.[32-34] Besides all measured covariates, we included the event indicator and the Nelson-Aalen estimator of the cumulative hazard to the survival time in the imputation model.[35] This analysis was also performed stratified for age groups and sex (men or women ≤65 years, men or women 65-80 years and men or women >80 years).

Finally, propensity scores were calculated for all patients, who were then stratified in four propensity score groups containing an equal amount of patients (0.0–0.18, 0.18–0.28, 0.28–0.49 and

0.49–1.00). The propensity score described the chance of filling prescriptions for antiplatelet, antihypertensive and statin therapy within 180 days after hospital discharge for each patient and was computed based on a logistic regression analysis including the following prognostic factors; sex, age, Charlson score, diabetes, atrial fibrillation, former AMI, hypertension, former stroke, intermittent claudication, stroke severity, smoking, alcohol, type of residence, civil status, in-hospital antithrombotic therapy, in-hospital anticoagulant therapy and socioeconomic status. This analysis was made in order to examine effectiveness among patients with similar chance of starting secondary prophylactic treatment. We analysed data with Stata 10.1 (StataCorp LP, Collage Station, TX, USA).

Results

Table 1 shows the characteristics of the 28 612 patients with ischemic stroke admitted to hospital between January 2003 and end June 2006.

During the follow-up study period of up to 5 years, we recorded 7462 deaths, 837 AMIs and 2658 recurrent stroke events in the entire study population, with mean follow-up times of 970 days, 956 days and 914 days respectively. Figure 1 show the cumulative incidence of death, AMI and recurrent stroke events for the 28 612 patients with ischemic stroke. The cumulative incidence after 5 years follow-up was 37.6% (95%CI 36.0–39.3%) for death, 3.9% (95%CI 3.5%–4.4%) for AMI and 11.7% (95%CI 10.9%–12.5%) for recurrent stroke.

Effectiveness of medical prophylaxis

Table 2 displays the crude and adjusted MRRs and HRs for AMI and recurrent stroke according to use of secondary medical prophylaxis.

Mortality

The overall adjusted MRRs ranged from 0.36–0.85 for treatment compared to no treatment for the seven examined drug groups. All relative risk estimates were statistical significant. While associated with a lower risk of death for all age and sex groups, the effectiveness of antiplatelet therapy had an inverse association with increasing age, i.e. the adjusted MRRs for men and women ≤65 years were 0.45 (95% confidence interval (CI) 0.38–0.53) and 0.58 (95%CI 0.44–0.76) respectively, compared to the adjusted MRRs for men and women >80 years which were 0.80 (0.71–0.90) and 0.83 (0.75–0.90) respectively. In contrast, the age- and sex-stratified analysis showed that effectiveness of oral anticoagulant therapy in patients with atrial fibrillation was positively associated with increasing age; the adjusted MRRs were 0.70 (95%CI 0.35–1.35) and 0.78 (95%CI 0.31-1.96) in men and women ≤65 years, respectively, compared to 0.41 (95%CI 0.30–0.55) and 0.35 (95%CI 0.28–0.45) in men and women >80 years, respectively. No systematic differences were found for the remaining drugs when stratifying the analyses according to age and sex (data not shown). In the propensity score stratified analysis, the adjusted MRRs in the four strata ranged from 0.40 (95%CI 0.36–0.46) to 0.94 (95%CI 0.87–1.01) for all drugs, with the lowest risk estimates in the strata with the highest propensity scores (data not shown).

Acute myocardial infarction

The overall adjusted HRs for AMI ranged from 0.80–1.39 for treatment compared to no treatment for the seven drugs examined. Although not all statistically significant, all adjusted HRs were below 1.00, except for beta blockers and calcium blockers (table 2). Overall the adjusted age- and sex-stratified analyses displayed a similar pattern, with only small differences between age- and sex-strata (data not shown).

In the propensity score stratified sub analysis the adjusted HRs ranged from 0.81 (95%CI 0.60–1.08) to 1.34 (95%CI 1.03–1.73). No systematic pattern was observed since for four drug groups (antiplatelets, oral anticoagulants, ACE inhibitors/ATII antagonists and beta blockers) the lowest risk estimates were found in the strata with the highest propensity scores, whereas the opposite pattern was found among the remaining three drug groups (calcium blockers, thiazide diuretics and statins) (data not shown).

Recurrent stroke

The overall adjusted HRs for recurrent stroke ranged from 0.58–1.14 for treatment compared to no treatment for the seven drug groups examined; use of oral anticoagulants (adjusted HR 0.58 (95%CI 0.46–0.73)) and statins (adjusted HR 0.84 (95%CI 0.77-0.91)) was associated with a lower risk of recurrent stroke. In contrast, use of beta blockers (adjusted HR 1.13 (95%CI 1.02–1.24)) and and thiazide diuretics (adjusted HR 1.14 (95%CI 1.03–1.26)) was associated with an increased risk of recurrent stroke. The age- and sex-stratified analyses displayed only minor differences across the age- and sex- strata (data not shown). Similarly, no systematic differences were found in the propensity score stratified analysis.

Discussion

In this nationwide follow-up study, we found an overall strong association between use of secondary medical prophylaxis and mortality and for selected drugs also an association with lower risk of hospitalization with AMI and recurrent stroke events in patients with ischemic stroke

following hospital discharge. For some drugs, this effectiveness varied by sex and even more so by age.

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. Furthermore, our analyses were based on a large cohort, with detailed information on all individuals in terms of clinical and sociodemographic characteristics, quality of in-hospital stroke care, and use of medical prophylaxis after hospital discharge, which limited the risk of confounding and chance findings.

The use of data collected during routine clinical work is a limitation that potentially affects the accuracy of the data. However, participation in the DNIP is mandatory for all departments treating patients with acute stroke in Denmark, and a systematic effort is made to ensure the validity of the DNIP [22]. 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.

We used prescription data as an indicator of drug use, but had no information on the actual patient compliance in our study (i.e. if the patient used all of the prescribed drugs). This could potentially introduce a misclassification into the study. However, the data are likely to give a good reflection of the actual drug use, since we only included data on prescriptions that had been filled and because the patients were only partly reimbursed. Furthermore, we assumed a standard prescription length of 90 days for each prescription filled. The possible misclassification introduced by these assumptions would most likely have biased our risk estimates towards the null, thereby underestimating the true effect of the drugs in question.

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).

For some drugs, we found use to be associated with a higher risk of AMI (beta blockers and calcium blockers) and recurrent stroke (antiplatelets, beta blockers and thiazide diuretics). These findings may potentially reflect residual confounding by indication (e.g. beta blockers and calcium blockers are often used in patients with known ischemic heart disease and use of these drugs could therefore be a marker of an underlying high risk of AMI) or the apparent effectiveness in relation to mortality which will increase the amount of time that the patients are at risk of an AMI or a recurrent stroke.

Comparison with other studies

Effectiveness in secondary prophylaxis of antiplatelet therapy has been investigated in three recent Chinese publications.[8-10] The first two studies from 2009 and 2010, the authors found that antiplatelet therapy was associated with a decreased risk of all-cause death, recurrent cerebrovascular events and any further vascular events following ischemic stroke.[8, 9] Similarly we found antiplatelet therapy to be associated with a lower mortality, whereas use of antiplatelets was not associated with a lower risk of AMI and recurrent stroke. The third study from 2010 found that antiplatelet therapy was associated with a reduced risk of death within one year after stroke in women (adjusted HR 0.55 95%CI: 0.37-0.83 with no treatment as reference), while this association was not found for men (estimate not presented in the paper). We could not confirm the existence of such a sex-related difference in effectiveness of antiplatelet therapy in the present study. However

in accordance with a meta-analysis based on 12 trials by van Walraven et al from 2009[36], antiplatelet therapy also appeared relatively less effective with increasing age in our study.

The effectiveness of oral anticoagulant therapy have primarily been examined in relation to primary stroke prophylaxis.[37-42] All of the studies have reported oral anticoagulant therapy among patients with atrial fibrillation to be associated with a lower risk of ischemic stroke. This is in accordance with our study where use of oral anticoagulants was associated with a lower risk of recurrent stroke events. In addition we also found use of oral anticoagulants to be associated with a lower risk of all cause death and AMI in our population, although our finding was not statistically significant for AMI. Also, while the meta-analysis by van Walraven et al found the efficacy of oral anticoagulants to be unchanged with increasing age, we found the association that oral anticoagulants appeared to be more effective with increasing age.

The effectiveness of antihypertensive therapy appears mainly to have been investigated in relation to primary stroke prophylaxis [43, 44], with an exception of the previous Chinese study from 2010 which found that antihypertensive treatment was associated with a lower mortality after one year.[10] This is in accordance to our findings that either of the antihypertensive drugs were associated with significantly lower MRRs. Two other studies found an association between use of non thiazide antihypertensives and an increased initial stroke severity and risk of stroke.[43, 44] We did not find this association for recurrent stroke events. However, we did find a similar pattern for AMI where use of antihypertensives other than thiazide diuretics was associated with a higher AMI risk. For beta blocker therapy and thiazide diuretic therapy we found that use was associated with the risk of recurrent stroke events.

Two recent studies have focused on the secondary prophylaxis with statins in stroke patients.[9, 11] Both of these studies found that statin therapy was associated with a lower risk of new vascular

events in patients admitted with stroke, however none of the results were statistically significant. In the present study, we also found that statin therapy was effective in reducing the risk of both AMI and recurrent stroke events; however, we also found that is was effective in reducing the risk of all-cause death, and our estimates were statistically significant for all three outcomes.

Existing investigations into effectiveness of medical prophylactic treatment in relation to stroke are few, and the numbers of studies on secondary medical prophylaxis are even fewer. Also, many of the studies are small, have incomplete follow-up or lack detailed information on patient prognostic factors and some use inclusion criteria or study populations that could reduce their external validity.

In conclusion, we found that a good overall effectiveness of secondary medical prophylaxis in preventing death of any cause and to some extent in preventing AMI and recurrent stroke events in patients with ischemic stroke following hospital discharge. For some drugs, this effectiveness varied by age but not sex. This study show that the efficacy of secondary medical prophylaxis in stroke patients documented in clinical trials overall appear to translate well into everyday clinical practice.

Funding Sources

Supported by grants from the Aarhus University Research Foundation.

Disclosures

None

Acknowledgements

None

Reference List

(1) Adams HP, Jr., del ZG, Alberts MJ, Bhatt DL, Brass L, Furlan A, Grubb RL, Higashida RT, Jauch EC, Kidwell C, Lyden PD, Morgenstern LB, Qureshi AI, Rosenwasser RH, Scott PA, Wijdicks EF. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Stroke* 2007 May;38(5):1655-711.

(2) Adams RJ, Albers G, Alberts MJ, Benavente O, Furie K, Goldstein LB, Gorelick P, Halperin J, Harbaugh R, Johnston SC, Katzan I, Kelly-Hayes M, Kenton EJ, Marks M, Sacco RL, Schwamm LH. Update to the AHA/ASA recommendations for the prevention of stroke in patients with stroke and transient ischemic attack. *Stroke* 2008 May;39(5):1647-52.

(3) ESO Guidelines for Stroke Management - January 2009. http://www.eso-stroke.org/recommendations.php?cid=9&sid=1. 2009.
Ref Type: Generic

(4) Zahn R, Schiele R, Seidl K, Bergmeier C, Haase KK, Glunz HG, Hauptmann KE, Voigtlander T, Gottwik M, Senges J. Primary percutaneous transluminal coronary angioplasty for acute myocardial infarction in patients not included in randomized studies. Maximal Individual Therapy in Acute Myocardial Infarction (MITRA) Study Group. *Am J Cardiol* 1999 May 1;83(9):1314-9.

(5) Heiat A, Gross CP, Krumholz HM. Representation of the elderly, women, and minorities in heart failure clinical trials. *Arch Intern Med* 2002 August 12;162(15):1682-8.

(6) Lee PY, Alexander KP, Hammill BG, Pasquali SK, Peterson ED. Representation of elderly persons and women in published randomized trials of acute coronary syndromes. *JAMA* 2001 August 8;286(6):708-13.

(7) Maasland L, van Oostenbrugge RJ, Franke CF, Scholte Op Reimer WJ, Koudstaal PJ, Dippel DW. Patients enrolled in large randomized clinical trials of antiplatelet treatment for prevention after transient ischemic attack or ischemic stroke are not representative of patients in clinical practice: the Netherlands Stroke Survey. *Stroke* 2009 August;40(8):2662-8.

(8) Ding D, Lu CZ, Fu JH, Hong Z. Association of antiplatelet therapy with lower risk of death and recurrent cerebrovascular events after ischemic stroke--results from the China Ischemic Stroke Registry Study. *Circ J* 2009 December;73(12):2342-7.

(9) Ding D, Lu CZ, Fu JH, Hong Z. Predictors of vascular events after ischemic stroke: the china ischemic stroke registry study. *Neuroepidemiology* 2010;34(2):110-6.

(10) Kong FY, Tao WD, Hao ZL, Liu M. Predictors of one-year disability and death in Chinese hospitalized women after ischemic stroke. *Cerebrovasc Dis* 2010 February;29(3):255-62.

(11) Lingsma HF, Steyerberg EW, Scholte Op Reimer WJ, van DR, Dippel DW. Statin treatment after a recent TIA or stroke: is effectiveness shown in randomized clinical trials also observed in everyday clinical practice? *Acta Neurol Scand* 2009 December 28.

(12) Lamassa M, Di CA, Pracucci G, Basile AM, Trefoloni G, Vanni P, Spolveri S, Baruffi MC, Landini G, Ghetti A, Wolfe CD, Inzitari D. Characteristics, outcome, and care of stroke associated with atrial fibrillation in Europe: data from a multicenter multinational hospital-based registry (The European Community Stroke Project). *Stroke* 2001 February;32(2):392-8.

(13) Ovbiagele B, Saver JL, Bang H, Chambless LE, Nassief A, Minuk J, Toole JF, Crouse JR. Statin treatment and adherence to national cholesterol guidelines after ischemic stroke. *Neurology* 2006 April 25;66(8):1164-70.

(14) Lalouschek W, Lang W, Greisenegger S, Mullner M. Determination of lipid profiles and use of statins in patients with ischemic stroke or transient ischemic attack. *Stroke* 2003 January;34(1):105-10.

(15) Fairhead JF, Rothwell PM. Underinvestigation and undertreatment of carotid disease in elderly patients with transient ischaemic attack and stroke: comparative population based study. *BMJ* 2006 September 9;333(7567):525-7.

(16) Smith DB, Murphy P, Santos P, Phillips M, Wilde M. Gender differences in the Colorado Stroke Registry. *Stroke* 2009 April;40(4):1078-81.

(17) Reeves MJ, Fonarow GC, Zhao X, Smith EE, Schwamm LH. Quality of care in women with ischemic stroke in the GWTG program. *Stroke* 2009 April;40(4):1127-33.

(18) Holroyd-Leduc JM, Kapral MK, Austin PC, Tu JV. Sex differences and similarities in the management and outcome of stroke patients. *Stroke* 2000 August;31(8):1833-7.

(19) Simpson CR, Wilson C, Hannaford PC, Williams D. Evidence for age and sex differences in the secondary prevention of stroke in Scottish primary care. *Stroke* 2005 August;36(8):1771-5.

(20) Palnum KD, Petersen P, Sorensen HT, Ingeman A, Mainz J, Bartels P, Johnsen SP. Older patients with acute stroke in Denmark: quality of care and short-term mortality. A nationwide follow-up study. *Age Ageing* 2008 January;37(1):90-5.

(21) Pedersen CB, Gotzsche H, Moller JO, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. *Dan Med Bull* 2006 November;53(4):441-9.

(22) Mainz J, Krog BR, Bjornshave B, Bartels P. Nationwide continuous quality improvement using clinical indicators: the Danish National Indicator Project. *Int J Qual Health Care* 2004 April;16 Suppl 1:i45-i50.

(23) The World Health Organization MONICA Project (monitoring trends and determinants in cardiovascular disease): a major international collaboration. WHO MONICA Project Principal Investigators. *J Clin Epidemiol* 1988;41(2):105-14.

(24) Multicenter trial of hemodilution in ischemic stroke--background and study protocol. Scandinavian Stroke Study Group. *Stroke* 1985 September;16(5):885-90.

(25) Lindenstrøm L, Boysen G, Christiansen LW, á Rogvi-Hansen B, Nielsen PW. Reliability of Scandinavian Neurological Stroke Scale. *Cerebrovasc Dis* 1991;1(2):103-7.

(26) Ingeman A, Pedersen L, Hundborg HH, Petersen P, Zielke S, Mainz J, Bartels P, Johnsen SP. Quality of care and mortality among patients with stroke: a nationwide follow-up study. *Med Care* 2008 January;46(1):63-9.

(27) Andersen TF, Madsen M, Jorgensen J, Mellemkjoer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999 June;46(3):263-8.

(28) Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992 June;45(6):613-9.

(29) Goldstein LB, Samsa GP, Matchar DB, Horner RD. Charlson Index comorbidity adjustment for ischemic stroke outcome studies. *Stroke* 2004 August;35(8):1941-5.

(30) Charlson ME, Pompei P, Ales KL, Mackenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40(5):373-83.

(31) Statistics Denmark. *Statistics Denmark's Classification of Occupational Skills*. 1 ed. Copenhagen: 1996.

(32) Royston P. Multiple imputation of missing values. *The Stata Journal 4* 2004;227-41.

(33) Royston P. Multiple imputation of missing values: update. *The Stata Journal 5* 2005;188-201.

(34) Royston P. Multiple imputation of missing values: update of ice. *The Stata Journal 5* 2005;527-36.

(35) White IR, Royston P. Imputing missing covariate values for the Cox model. *Stat Med* 2009 July 10;28(15):1982-98.

(36) van WC, Hart RG, Connolly S, Austin PC, Mant J, Hobbs FD, Koudstaal PJ, Petersen P, Perez-Gomez F, Knottnerus JA, Boode B, Ezekowitz MD, Singer DE. Effect of age on stroke prevention therapy in patients with atrial fibrillation: the atrial fibrillation investigators. *Stroke* 2009 April;40(4):1410-6.

(37) Go AS, Hylek EM, Chang Y, Phillips KA, Henault LE, Capra AM, Jensvold NG, Selby JV, Singer DE. Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? *JAMA* 2003 November 26;290(20):2685-92.

(38) Darkow T, Vanderplas AM, Lew KH, Kim J, Hauch O. Treatment patterns and real-world effectiveness of warfarin in nonvalvular atrial fibrillation within a managed care system. *Curr Med Res Opin* 2005 October;21(10):1583-94.

(39) Birman-Deych E, Radford MJ, Nilasena DS, Gage BF. Use and effectiveness of warfarin in Medicare beneficiaries with atrial fibrillation. *Stroke* 2006 April;37(4):1070-4.

(40) Lakshminarayan K, Solid CA, Collins AJ, Anderson DC, Herzog CA. Atrial fibrillation and stroke in the general medicare population: a 10-year perspective (1992 to 2002). *Stroke* 2006 August;37(8):1969-74.

(41) Parkash R, Wee V, Gardner MJ, Cox JL, Thompson K, Brownell B, Anderson DR. The impact of warfarin use on clinical outcomes in atrial fibrillation: a population-based study. *Can J Cardiol* 2007 May 1;23(6):457-61.

(42) Fang MC, Singer DE, Chang Y, Hylek EM, Henault LE, Jensvold NG, Go AS. Gender differences in the risk of ischemic stroke and peripheral embolism in atrial fibrillation: the AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) study. *Circulation* 2005 September 20;112(12):1687-91.

(43) Klungel OH, Heckbert SR, Longstreth WT, Jr., Furberg CD, Kaplan RC, Smith NL, Lemaitre RN, Leufkens HG, de BA, Psaty BM. Antihypertensive drug therapies and the risk of ischemic stroke. *Arch Intern Med* 2001 January 8;161(1):37-43.

(44) Yu AY, Keezer MR, Zhu B, Wolfson C, Cote R. Pre-stroke use of antihypertensives, antiplatelets, or statins and early ischemic stroke outcomes. *Cerebrovasc Dis* 2009;27(4):398-402.

Table 1: Characteristics of 28 612 patients admitted with ischemic stroke in Denmark, 2003-2006.

	N	Percentage
Sex		
Male	15 167	53.0
Female	13 445	47.0
Age		
≤65	9008	31.5
65-80	12 171	42.5
>80	7433	26.0
Co-morbidity		
Charlson Index		
None (0 pt)	13 255	46.3
Low (1-2 pt)	10 941	38.2
High (>2 pt)	4416	15.4
Diabetes Mellitus		
Yes	3796	13.3
No	23 060	80.6
Undisclosed	1539	5.4
Atrial Fibrillation		
Yes	4174	14.6
No	22 417	78.3
Undisclosed	1791	6.3
AMI		
Yes	2600	9.1
No	23 817	83.2
Undisclosed	1965	6.9
Hypertension		

Yes	12 632	44.1
No	13 634	47.7
Undisclosed	2141	7.5
Former Stroke		
Yes	6239	21.8
No	20 488	71.6
Undisclosed	1667	5.8
Intermittant Claudication		
Yes	1087	3.8
No	23 616	82.5
Undisclosed	3629	12.7
Stroke Severity (SSS)		
Very Severe (0-14 pt)	1390	4.9
Severe (15-29 pt)	2068	7.2
Moderate (30-44 pt)	4882	17.1
Mild (45-58 pt)	16 229	56.7
Smoking		
Daily	10 076	35.2
Occasionally	464	1.6
Ex- smoker (more than 6 months)	5222	18.3
Never smoked	8334	29.1
Undisclosed	4222	14.8
Alchohol		
14/21 drinks/week or less	22 258	77.8
More than 14/21 drinks-/week	1987	6.9

Undisclosed	4059	14.2
Type of Residence		
Own residence	24 630	86.1
Care home	1501	5.2
Other	558	2.0
Undisclosed	1651	5.8
Civil Status		
Co-habitant	15 074	52.7
Lives alone	11 582	40.5
Other	563	2.0
Undisclosed	1150	4.0
Percentage of fulfilled indicators		
<50%	6231	21.8
50%-99%	13 548	47.4
100%	8741	30.6
Socio economic status		
Self-employed with employees	217	0.8
Self-employed without employees	559	2.0
Top managers	147	0.5
Salaried employees, upper level	459	1.6
Salaried employees, intermediate level	630	2.2
Salaried employees, basic level	1626	5.7
Salaried employees, other	542	1.9
Employees, not further specified	829	2.9

Assisting spouses	35	0.1
Unemployed	414	1.4
Disability supplement	2527	8.8
Old-age pensioners	18 023	63.0
Early retirement benefit	1805	6.3
Other economically inactive persons	266	0.9
Other	451	1.5

Figure 1: Cumulative Incidences with confidence intervals (CI) of death, acute myocardial infarction and recurrent stroke following hospital discharge among 28 612 patients with ischemic stroke from January 2003 till end December 2007.

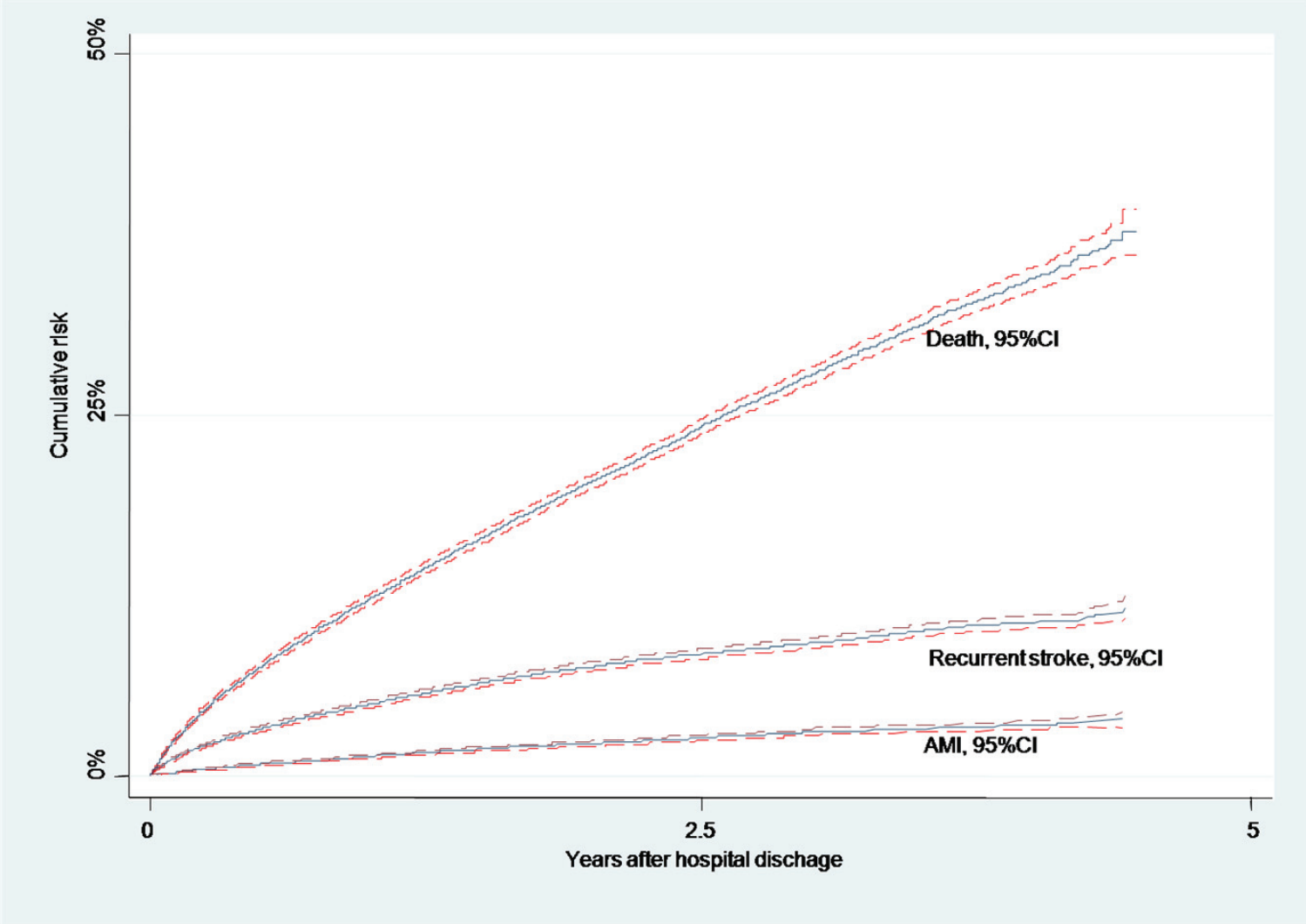


Table 2. Crude and adjusted risk of death, AMI and recurrent stroke according to use of secondary medical prophylaxis.

		N	Death Crude (MRR 95% CI)	Death Adjusted (MRR 95% CI)†	N	AMI Crude (HR 95% CI)	AMI Adjusted (HR 95% CI)	N	Recurrent stroke Crude (HR 95% CI)	Recurrent stroke Adjusted (HR 95% CI)
Antiplatelets										
	No	3134	1.00 (ref)	1.00 (ref)	3232	1.00 (ref)	1.00 (ref)	3488	1.00 (ref)	1.00 (ref)
	Yes	25 478	0.65 (0.62-0.68)	0.74 (0.71-0.78)	25 380	0.96 (0.82-1.13)	0.98 (0.83-1.15)	25 124	1.03 (0.94-1.12)	1.05 (0.96-1.15)
Oral anticoagulants*										
	No	1989	1.00 (ref)	1.00 (ref)	2002	1.00 (ref)	1.00 (ref)	2029	1.00 (ref)	1.00 (ref)
	Yes	2185	0.28 (0.25-0.32)	0.36 (0.32-0.41)	2172	0.73 (0.52-1.03)	0.78 (0.55-1.12)	2145	0.56 (0.45-0.69)	0.58 (0.46-0.73)
ACE Inhibitors/ATII antagonists										
	No	15 179	1.00 (ref)	1.00 (ref)	15 348	1.00 (ref)	1.00 (ref)	15 549	1.00 (ref)	1.00 (ref)
	Yes	13 433	0.66 (0.62-0.69)	0.67 (0.64-0.71)	13 264	1.14 (0.99-1.32)	0.93 (0.80-1.08)	13 063	1.00 (0.92-1.09)	0.94 (0.86-1.02)
Beta blockers										
	No	19 345	1.00 (ref)	1.00 (ref)	19 657	1.00 (ref)	1.00 (ref)	19 607	1.00 (ref)	1.00 (ref)
	Yes	9267	0.98 (0.92-1.04)	0.85 (0.80-0.90)	8955	1.84 (1.58-2.13)	1.39 (1.18-1.62)	9005	1.22 (1.11-1.34)	1.13 (1.02-1.24)
Calcium Blockers										
	No	20 538	1.00 (ref)	1.00 (ref)	20 630	1.00 (ref)	1.00 (ref)	20 821	1.00 (ref)	1.00 (ref)
	Yes	8074	0.78 (0.73-0.83)	0.75 (0.70-0.80)	7982	1.27 (1.06-1.50)	1.05 (0.88-1.26)	7791	1.08 (0.98-1.20)	1.00 (0.90-1.12)
Thiazide Diuretics										
	No	18 973	1.00 (ref)	1.00 (ref)	19 044	1.00 (ref)	1.00 (ref)	19 296	1.00 (ref)	1.00 (ref)

	Yes	9639	0.77 (0.73-0.83)	0.82 (0.77-0.88)	9568	0.79 (0.65-0.96)	0.79 (0.65-0.97)	9316	1.15 (1.03-1.27)	1.14 (1.03-1.26)
Statins										
	No	11 354	1.00 (ref)	1.00 (ref)	11 546	1.00 (ref)	1.00 (ref)	11 837	1.00 (ref)	1.00 (ref)
	Yes	17 258	0.35 (0.32-0.37)	0.41 (0.39-0.44)	17 066	0.86 (0.75-0.99)	0.80 (0.69-0.92)	16 775	0.84 (0.77-0.91)	0.84 (0.77-0.91)

* Patients with known AFLI during hospitalization only

† 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 and civil status)

Reports and PhD theses from Department of Clinical Epidemiology

1. Ane Marie Thulstrup: Mortality, infections and operative risk in patients with liver cirrhosis in Denmark. Clinical epidemiological studies. *2000*.

2. Nana Thrane: Prescription of systemic antibiotics for Danish children. *2000*.

3. Charlotte Søndergaard. Follow-up studies of prenatal, perinatal and postnatal risk factors in infantile colic. *2001*.

4. Charlotte Olesen: Use of the North Jutland Prescription Database in epidemiological studies of drug use and drug safety during pregnancy. *2001*.

5. Yuan Wei: The impact of fetal growth on the subsequent risk of infectious disease and asthma in childhood. *2001*.

6. Gitte Pedersen. Bacteremia: treatment and prognosis. *2001*.

7. Henrik Gregersen: The prognosis of Danish patients with monoclonal gammopathy of undertermined significance: register-based studies. *2002*.

8. Bente Nørgård: Colitis ulcerosa, coeliaki og graviditet; en oversigt med speciel reference til forløb og sikkerhed af medicinsk behandling. *2002*.

9. Søren Paaske Johnsen: Risk factors for stroke with special reference to diet, Chlamydia pneumoniae, infection, and use of non-steroidal anti-inflammatory drugs. *2002*.

10. Elise Snitker Jensen: Seasonal variation of meningococcal disease and factors associated with its outcome. *2003*.

11. Andrea Floyd: Drug-associated acute pancreatitis. Clinical epidemiological studies of selected drugs. *2004*.

12. Pia Wogelius: Aspects of dental health in children with asthma. Epidemiological studies of dental anxiety and caries among children in North Jutland County, Denmark. *2004*.

13. Kort-og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme i Nordjyllands, Viborg og Århus amter 1985-2003. *2004*.

14. Reimar W. Thomsen: Diabetes mellitus and community-acquired bacteremia: risk and prognosis. *2004*.

15. Kronisk obstruktiv lungesygdom i Nordjyllands, Viborg og Århus amter 1994-2004. Forekomst og prognose. Et pilotprojekt. *2005*.

16. Lungebetændelse i Nordjyllands, Viborg og Århus amter 1994-2004. Forekomst og prognose. Et pilotprojekt. *2005*.

17. Kort- og langtidsoverlevelse efter indlæggelse for nyre-, bugspytkirtel- og leverkræft i Nordjyllands, Viborg, Ringkøbing og Århus amter 1985-2004. *2005*.

18. Kort- og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme i Nordjyllands, Viborg, Ringkøbing og Århus amter 1995-2005. *2005*.

19. Mette Nørgaard: Haematological malignancies: Risk and prognosis. *2006*.

20. Alma Becic Pedersen: Studies based on the Danish Hip Arthroplastry Registry. *2006*.

    Særtryk: Klinisk Epidemiologisk Afdeling - De første 5 år. *2006*.

21. Blindtarmsbetændelse i Vejle, Ringkjøbing, Viborg, Nordjyllands og Århus Amter. *2006*.

22. Andre sygdommes betydning for overlevelse efter indlæggelse for seks kræftsygdomme i Nordjyllands, Viborg, Ringkjøbing og Århus amter 1995-2005. *2006*.

23. Ambulante besøg og indlæggelser for udvalgte kroniske sygdomme på somatiske hospitaler i Århus, Ringkjøbing, Viborg, og Nordjyllands amter. *2006*.

24. Ellen M Mikkelsen: Impact of genetic counseling for hereditary breast and ovarian cancer disposition on psychosocial outcomes and risk perception: A population-based follow-up study. *2006*.

25. Forbruget af lægemidler mod kroniske sygdomme i Århus, Viborg og Nordjyllands amter 2004-2005. *2006*.

26. Tilbagelægning af kolostomi og ileostomi i Vejle, Ringkjøbing, Viborg, Nordjyllands og Århus Amter. *2006*.

27. Rune Erichsen: Time trend in incidence and prognosis of primary liver cancer and liver cancer of unknown origin in a Danish region, 1985-2004. *2007*.

28. Vivian Langagergaard: Birth outcome in Danish women with breast cancer, cutaneous malignant melanoma, and Hodgkin's disease. *2007*.

29. Cynthia de Luise: The relationship between chronic obstructive pulmonary disease, comorbidity and mortality following hip fracture. *2007*.

30. Kirstine Kobberøe Søgaard: Risk of venous thromboembolism in patients with liver disease: A nationwide population-based case-control study. *2007*.

31. Kort- og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme i Region Midtjylland og Region Nordjylland 1995-2006. *2007*.

32. Mette Skytte Tetsche: Prognosis for ovarian cancer in Denmark 1980-2005: Studies of use of hospital discharge data to monitor and study prognosis and impact of comorbidity and venous thromboembolism on survival. *2007*.

33. Estrid Muff Munk: Clinical epidemiological studies in patients with unexplained chest and/or epigastric pain. *2007*.

34. Sygehuskontakter og lægemiddelforbrug for udvalgte kroniske sygdomme i Region Nordjylland. *2007*.

35. Vera Ehrenstein: Association of Apgar score and postterm delivery with neurologic morbidity: Cohort studies using data from Danish population registries. *2007*.

36. Annette Østergaard Jensen: Chronic diseases and non-melanoma skin cancer. The impact on risk and prognosis. *2008*.

37. Use of medical databases in clinical epidemiology. *2008*.

38. Majken Karoline Jensen: Genetic variation related to high-density lipoprotein metabolism and risk of coronary heart disease. *2008*.

39. Blodprop i hjertet - forekomst og prognose. En undersøgelse af førstegangsindlæggelser i Region Nordjylland og Region Midtjylland. *2008*.

40. Asbestose og kræft i lungehinderne. Danmark 1977-2005. *2008*.

41. Kort- og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme i Region Midtjylland og Region Nordjylland 1996-2007. *2008*.

42. Akutte indlæggelsesforløb og skadestuebesøg på hospiter i Region Midtjylland og Region Nordjylland 2003-2007. Et pilotprojekt. *2009*.

43. Peter Jepsen: Prognosis for Danish patients with liver cirrhosis. *2009*.

44. Lars Pedersen: Use of Danish health registries to study drug-induced birth defects – A review with special reference to methodological issues and maternal use of non-steroidal anti-inflammatory drugs and Loratadine. *2009*.

45. Steffen Christensen: Prognosis of Danish patients in intensive care. Clinical epidemiological studies on the impact of preadmission cardiovascular drug use on mortality. *2009*.

46. Morten Schmidt: Use of selective cyclooxygenase-2 inhibitors and nonselective nonsteroidal antiinflammatory drugs and risk of cardiovascular events and death after intracoronary stenting. *2009*.

47. Jette Bromman Kornum: Obesity, diabetes and hospitalization with pneumonia. *2009*.

48. Theis Thilemann: Medication use and risk of revision after primary total hip arthroplasty. *2009*.

49. Operativ fjernelse af galdeblæren. Region Midtjylland & Region Nordjylland. 1998-2008. *2009*.

50. Mette Søgaard: Diagnosis and prognosis of patients with community-acquired bacteremia. *2009*.

51. Marianne Tang Severinsen. Risk factors for venous thromboembolism: Smoking, anthropometry and genetic susceptibility. *2010*.

52. Henriette Thisted: Antidiabetic Treatments and ischemic cardiovascular disease in Denmark: Risk and outcome. *2010*.

53. Kort- og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme. Region Midtjylland og Region Nordjylland 1997-2008. *2010*.

54. Prognosen efter akut indlæggelse på Medicinsk Visitationsafsnit på Nørrebrogade, Århus Sygehus. *2010*.