Early stroke care

Studies on structure, process, and outcome

PhD thesis

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PREFACE

This thesis is a result of three years work at the Department of Clinical Epidemiology, Aarhus University Hospital, Denmark. It has been a pleasure to work at the department which provides a dynamic work environment, extensive expertise in working with clinical databases, and continuous training in clinical epidemiology.

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TABLE OF CONTENTS

1. INTRODUCTION

Stroke has a high incidence, high mortality, high morbidity among the survivors, and high economic costs.[1] This has resulted in a global need for continuous monitoring and improvement of the quality of stroke care.[2-6] The Danish National Indicator Project aims at documenting and improving the quality of health care in Denmark at a national level for specific diseases, including stroke.[7] The basis for the studies in this thesis is the national stroke registry in the Danish National Indicator Project (DNIP-stroke). With roots in clinical epidemiology, this thesis aims at identifying links in health care quality focusing on overall associations between health care specialization, health care performance, and outcome in modern stroke care.

1.1. DEFINING STROKE

The World Health Organization (WHO) defines stroke as "rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin".[8] Stroke is a clinical syndrome with different pathologies.[9] It may be caused by an interruption of blood supply to the brain that results from either blockage by a blood clot or by narrowing (ischemic stroke) or by rupture of a blood vessel (hemorrhagic stroke).[1, 8] Ischemic stroke counts for approximately 80% of all strokes in most populations, intracerebral hemorrhage constitutes about 10%, and subarachnoid hemorrhage constitutes about 3% while the pathologic type of the remaining strokes are undefined.[9, 10] The clinical presentation of stroke depends on the affected brain structures and vascular territory, and varies substantially.[11] The clinical symptoms may include motor, sensory, and visual disturbances, altered level of consciousness, and neuropsychological symptoms.[11]

1.2. CONSEQUENCES OF STROKE

Stroke is a major public health concern. WHO estimates that 15 million people worldwide suffer a stroke each year.[1] Over the past four decades, the incidence of stroke has decreased by approximately 40% in high-income countries, but the absolute number of strokes continues to increase because of the ageing population.[1, 10] The decline in incidence has mainly been ascribed to better control of modifiable risk factors, including high blood pressure and smoking.[1, 12] However, the stroke incidence rates in low- to middle-income countries have now exceeded those in high-income countries.[10] During 2000-2008, the stroke incidence was 94 per 100,000 person-years in high-income countries and 117 per 100,000 person-years in low- to middle-income countries.[10]

1.2.1. Clinical outcome

In the acute phase, stroke causes immediate neurological damage and abrupt onset of neurological symptoms or death.[1, 11] Of the 15 million people worldwide who suffer a stroke each year, 5 million die and another 5 million are left permanently disabled.[1] This makes stroke the second leading cause of death worldwide for people above the age of 60.[13, 14] In recent decades, early (21-day to 1-month) case fatality has dropped, but is still up to 30% in high-income countries and 35% in low- and middle-income countries.[10] It is estimated that about 64%, 43%, and 24% of the patients survive up to 1, 5, and 10 years after a stroke, respectively.[15] Stroke survivors have a dramatic functional decline in the first two years after a stroke, and 10-20% of stroke survivors still have moderate to severe disability 10 years after the stroke.[15] Because many survivors remain disabled, stroke is a main cause of long-term neurological disability among the elderly.[16] Furthermore, between 20% and 30% of stroke survivors experience disability, inactivity, cognitive impairment, depression, anxiety, and/or reduced quality of life up to 10 years after a stroke.[15]

A previous stroke significantly increases the risk of future episodes although the annual stroke recurrence rate has declined substantially over the last four decades. Approximately 9% of patients per year had a recurrent stroke in the 1960s, and approximately 5% in the 2000s.[17] The decline in stroke recurrence has mainly been ascribed to improved blood pressure control and more frequent use of antiplatelet therapy.[17]

Stroke often requires prolonged hospitalization and rehabilitation, and a large proportion of the patients are readmitted because of recurrent ischemic stroke, heart failure, vascular events, pneumonia, or hip fracture.[18] Reports of readmission rates vary across studies, but are in general high. One-year all-cause readmissions range from about 30% to 63%, and one-year stroke-related readmissions range from 11% to 32%.[18, 19]

Stroke also represents a significant health care challenge in Denmark. Approximately 12,000-14,000 persons suffer a stroke each year, and 10-20% of them die during the first month after the stroke. In total, 30,000-40,000 persons live with disabilities after a stroke.[20-22]

1.2.2. Length of hospital stay and costs

Stroke has major costs for society, families, and the people who suffer a stroke. The direct costs of stroke may be defined as all the goods, services, and other resources that are consumed during the provision of healthcare in relation to stroke. This may include costs of hospital and nursing home care, the services of medical professionals, investigations, drugs, and inpatient as well as out-patient rehabilitation.[23, 24] The total costs of stroke also include indirect costs caused by production losses from inability to work.[23, 24] Stroke may also entail human (intangible) costs related to inactivity, depression, anxiety, and reduced quality of life.[15]

In developed countries, the direct costs of stroke account for 2-4% of the total health care expenditures.[24] However, the indirect costs from inability of work may be substantial, and health expenditure data including only the direct costs may underestimate the overall costs of stroke.[23] In developed countries, more than half of the direct costs during the first year after stroke are attributable to the acute hospitalization and inpatient rehabilitation,[23-25] and variation in the hospital costs is largely related to the length of hospital stay.[26] In stroke units, the direct costs of stroke are primarily dominated by the costs of nurse- and physician working time and hospital overheads, causing the direct costs to be closely related to length of the hospital stay.[27, 28]

In Denmark, the direct costs of stroke have been estimated to approximately DKK 2.7 billion based on patient-level cost estimations from 1995.[21, 29] This represented about 4% of the health care expenditure.[21] Recent numbers show that between 12,000 and 16,500 Danish hospital admissions are caused by stroke each year.[30, 31] A Danish study from 1995 estimated hospital care (until first discharge), including acute care and rehabilitation, to constitute approximately 70% of the total costs of health care and social services during the first year after stroke.[29] The costs of readmissions constituted approximately 40% of the costs from the time of hospital discharge until one year after the stroke.[29] However, these figures may not entirely reflect current stroke care, in part because of a general trend towards shorter length of hospital stay.[30]

1.2.3. Prognostic factors

Several factors may influence the outcome and costs of stroke. These include:

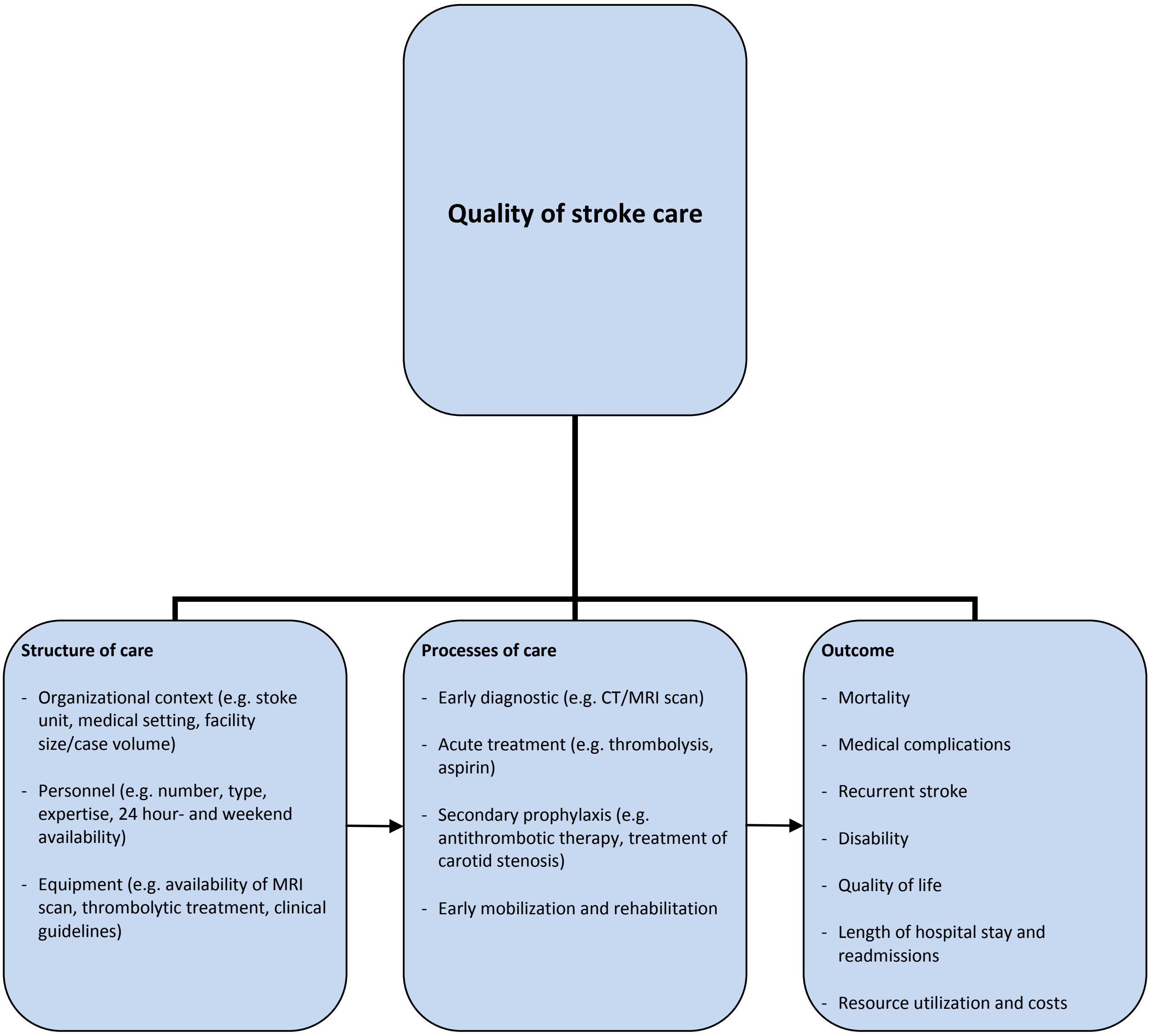
- The actual illness, e.g. stroke severity, and stroke subtype.[26, 32, 33]
- Patient characteristics, e.g. age, sex, marital status, disability before the current stroke, comorbid disease, lifestyle, hypertension, atrial fibrillation, and blood glucose.[26, 32, 33]
- Early diagnostics in order to initiate the right treatment.[11, 33]
- The medical care delivered, e.g. stroke unit care, thrombolysis, and antiplatelet or anticoagulant therapy.[33-37]
- Clinical performance, i.e. processes of care.[33, 38, 39]
- Patient compliance, e.g. compliance with specific interventions for stroke rehabilitation.[33, 40]

1.3. QUALITY OF CARE: BACKGROUND AND LITERATURE

It is a central objective in current health policy to ensure the best value for money by improving quality of health services and health outcomes at similar or less costs.[41, 42] This need has been reinforced by the current financial crisis, the rising costs of an aging population, and new medical advances.[41]

Quality of health care is traditionally characterized according to three dimensions: *structure*, *process*, and *outcome*. *Structure* refers to characteristics of the health care system, including the organizational context (e.g. medical setting), economic resources (e.g. budget constraints), material resources (e.g. equipment), and human resources (e.g. qualifications of personnel). Specialization in health care typically refers to the organization; i.e. structure, of care. Specialization concerns health care characteristics such as the medical specialty of physicians/departments, scaling up health care services, and focusing on specific treatments or diseases.[43-46] *Process* refers to how patient care strategies are applied, including initial evaluation at admission, early admission to a stroke unit, early initiation of rehabilitation, and prevention of recurrent strokes. *Outcome* refers to the effects of care on health status, including mortality, functional gains, hospital readmissions, changes in patient behavior, and satisfaction with care. In theory, these three dimensions interact so that optimal structure of care allows for improved processes of care, which in turn will affect outcome positively.[47, 48] Figure 1 displays a modified version of the Donabedian model of structure, process, and outcomes as a conceptual framework for the four studies in this thesis.[47, 48] The studies focus specifically on stroke unit characteristics (medical setting and case volume), processes of early stroke care, mortality, and hospital bed-day use, which may all be considered aspects of health care quality.

Figure 1. Modified Donabedian model[47, 48]



Monitoring the quality of stroke care has high priority internationally. A number of countries monitor the quality of stroke care at a national level in established clinical databases; e.g. Sweden[6], the United States[3], Canada[5], Germany[4], and Austria[2]. In Denmark, national clinical guidelines for the acute treatment and care of patient with stroke were first launched in 2003, and updated in 2005 and 2009. These guidelines recommend early initiation of treatment, care and rehabilitation, which is in line with international consensus guidelines from the American Heart Association and the European Stroke Initiative (EUSI).[49, 50] The DNIP-stroke registry monitors and documents on a national level whether several of these key recommendations for the early treatment and care of patients with stroke are followed by use of evidence-based quality of care indicators. A distinction is made between structure-, process-, and outcome indicators,[7, 51] and time limits are defined for each process indicator to capture the timeliness of care.[52] In the four studies of this thesis, *process indicators* will also be referred to as processes of care, and *early* care will refer to whether patients receive the processes of care within the defined time limits.

1.3.1. Search strategy

The strategy for searching the literature was primarily aimed at identifying evidence regarding the following relationships:

- The association between processes of early stroke care and resource utilization among patients with stroke
- The association between medical specialization and processes of care, clinical outcome, and resource utilization among patients with stroke
- The association between case volume and processes of care, clinical outcome, and resource utilization among patients with stroke

The electronic databases PubMed and The Cochrane Library were searched for studies published until September, 2011. The following terms were used alone or in combination: “Stroke”[Mesh], “Stroke/economics”[Majr], "Costs and Cost Analysis"[Majr], “Length of stay”[Mesh], “Hospital Costs”[Mesh], “Quality Indicators, Health Care”[Mesh], "Thrombolytic Therapy"[Mesh], "Stroke unit"(free-text), "Platelet Aggregation Inhibitors"[Mesh], "Anticoagulants"[Mesh], "Tomography, X-Ray Computed"[Mesh], "Magnetic Resonance Imaging"[Mesh], "Physical Therapy (Specialty)"[Mesh], "Occupational Therapy"[Mesh], "Nutrition Assessment"[Mesh], "Deglutition Disorders"[Mesh], "Constipation"[Mesh], "Early Ambulation"[Mesh], "Intermittent Urethral Catheterization"[Mesh], "Heparin"[Mesh], “Specialties, Medical”[Mesh], “Medical staff, Hospital”[Mesh], “Health Care Facilities, Manpower, and Services”[Mesh], “Hospital Bed

Capacity"[Mesh], "Health Facility Size"[Mesh], "Workload"[Mesh], and "Volume"(free-text). The searches were limited to include only publications in English and Danish and in humans. Only studies that applied patient-level data were selected. Additional studies were found by searching the reference lists from the identified publications. Furthermore, searches on the internet were performed on the web pages of WHO (www.who.int), Danish national health authorities (www.sst.dk, www.nip.dk), and Danish patient associations (www.hjernesagen.dk, www.hjerteforeningen.dk).

From the studies focusing specifically on the topics of the four studies in this thesis, data were extracted using a standardized form. Data extracted for each study included: country, patient population, study design, time period, exposure definition, main findings, and main study limitations (please see Table 1, 2, and 3).

The evidence regarding an association between processes of stroke care and clinical outcome is well-documented in a recent PhD dissertation and in documents from the Danish National Indicator Project.[52, 53] The evidence regarding the effect of stroke units is documented in a Cochrane Review which summarizes the evidence from 31 trials, involving 6,936 participants.[27, 35] Therefore, no literature search was performed on these topics.

1.3.2. Stroke units

Stroke patients are frequently admitted to hospital in the acute phase of stroke and may receive care in a variety of ways and in a range of settings.[27, 35, 54] However, the inhospital treatment setting, the composition of health care professionals, and the organization of care appear to be of major importance to the prognosis following a stroke. A Cochrane review showed that patients with stroke who received organized inpatient care in stroke units were more likely to be alive, independent, and living at home one year after the stroke compared with patients who received less organized care.[35] Stroke unit care may also result in a modest reduction in length of hospital stay.[35] All types of patients, irrespective of gender, age, stroke subtype, and stroke severity appear to benefit from stroke unit care.[35] Accordingly, current clinical guidelines recommend that all hospitals treating patients with stroke establish a specialized stroke unit, and that patients with acute stroke are admitted to inpatient care in stroke units.[49, 50] In Denmark, it is estimated that at least 80% of all patients with acute stroke are admitted to specialized stroke units.[22]

However, many questions remain unanswered about why stroke unit care improves outcome. The randomized controlled trials, documenting the effect of stroke unit care, included a mixture of both disease-specific services (dedicated stroke units) and generic disability services (mixed assessment/rehabilitation units) established within a variety of departments, including departments of general medicine, geriatric medicine, neurology, and rehabilitation medicine.[27] However, some common features characterized the stroke units. A specialized stroke unit was a hospital department/unit exclusively or primarily dedicated to patients with stroke and characterized by coordinated multidisciplinary rehabilitation, staff with specific interest in stroke, involvement of relatives, and continuous education and training of the staff.[55] Still, there is continuing uncertainty about what are the important components and practices within a stroke unit.[27]

1.3.3. Processes of care and outcome

Randomized controlled trials have demonstrated that some specific processes of care, including admission to specialized stroke units, early mobilization, and use of thrombolysis, antiplatelet drugs, and oral anticoagulants, have a beneficial effect on stroke outcome in terms of reduced mortality, disability, and institutionalization.[34-37, 56] Furthermore, a number of observational studies have linked higher quality of care, defined as delivering specific processes of care during hospitalization, with reduced risk of death and disability among patients with stroke[38, 57-61]. A positive association has been reported for overall guideline compliance in most studies[57, 58, 60], and some studies have reported positive associations for separate processes of care, e.g. initiation of antiplatelet therapy, swallowing assessment, and early mobilization[38, 39, 59, 61]. In the DNIP-stroke population which forms the basis of the studies in this thesis, higher quality of early stroke care in terms of receiving evidence-based processes of early stroke care has been linked with lower risk of death and medical complications.[38, 39]

Because in-hospital care and rehabilitation constitutes a major part of the direct costs of stroke,[23-25] randomized controlled studies have evaluated initiatives aimed at reducing the bed-day use in hospital. These initiatives include services for helping acute stroke patients avoid hospital admission and early supported discharge.[62, 63] However, there is growing interest in assessing whether improved health care performance can eliminate primarily wasteful costs; i.e. costs related to less successful patient outcome, extra work, or corrective work.[41, 42, 64, 65] The evidence suggests that improving quality of care may result in cost savings, possibly mediated through improved health.[65, 66] However, only few studies have examined how health care performance in terms of providing evidence-based processes of early care relate to resource utilization in patients with stroke. Table 1 summarizes the relevant literature.

The literature search identified eight studies assessing the association between processes of early stroke care and resource utilization based on patient-level data. The results concerning specialized stroke unit care are diverging and inconclusive. Most of the studies showed no statistically significant difference in total direct costs during the first 28 weeks to one year after a stroke when comparing stroke unit care with other care modalities; e.g. mobile stroke team and general medical wards.[67-69] However, the short-term costs of stroke are likely to be dominated by the length of hospital stay and the long-term costs are likely to be dominated by the need for nursing care, both of which is likely to be reduced when cared for in organized stroke units.[35] On the other hand, stroke units may incur slightly higher treatment and examination costs compared with conventional care.[27] Luengo-Fernandez et al.[70] focused on early, pre-hospital management of patients with minor stroke and transient ischemic attack who were not admitted directly to hospital in the acute phase of stroke. They showed that accelerated, immediate pre-hospital diagnostic evaluation and treatment in an outpatient clinic was associated with reduced in-hospital bed-day use and reduced hospital costs during 90-days follow-up. This intervention was compared with scheduled diagnostic evaluation in an outpatient clinic and subsequent treatment in hospital or by a general practitioner. Besides the mentioned studies on service interventions, some studies focused on the economic implications of overall guideline compliance and specific processes of care. Quaglini et al.[66] found that overall guideline compliance during the acute and sub-acute hospitalization was associated with hospital cost savings; and based on descriptive analyses, the cost savings were ascribed to shorter length of stay. The study evaluated a compliance rating of 47 processes of care recommended by the American Heart Association for different aspects of diagnostic, treatment, and care of patients with stroke.[60, 66] Furthermore, a study by Wilson et al.[71] suggested that acute treatment with blood pressure lowering drugs may be associated with reduced costs at 3-month follow-up in stroke patients with systolic blood pressure >160 mm Hg, although the result did not reach statistical significance. In addition, randomized controlled trials have suggested that early mobilization and treatment with thrombolysis in the acute phase of stroke may incur long-term cost savings.[72, 73] Except for the study by Luengo-Fernandez et al.,[70] all the referred studies included the costs of providing the intervention.[66-69, 71-73]

In summary, most of the available evidence suggests that providing early intensive stroke care may be cost neutral, and in some cases even cost saving.

Limitations of the existing studies: The timeliness of diagnostic evaluation, treatment, and rehabilitation in stroke care has received much attention in recent years due to a growing amount of evidence that early care has a beneficial effect on stroke outcome. This include early management policies in stroke units,[35, 54] early mobilization,[56, 74] and thrombolytic therapy[37]. However, little is known about the economic consequences of early care in relation to fulfillment of specific process criteria for a range of recommended, evidence-based processes of care among patients with stroke. Furthermore, the generalizability of most of the existing studies are limited by relatively small and restricted study populations, studies being more than 10 years old, and uncertainty about whether the study populations received care in specialized stroke units. In conclusion, the evidence is scarce as to whether early evidence-based care is related to resource utilization in modern stroke care.

Table 1. Summary of existing studies: processes of early stroke care and resource utilization (ordered by the year of follow-up)

Author, country	n, patients (institution)	Population	Study design	Follow-up	Processes of care	Main findings	Adjustment for stroke severity
Luengo-Fernandez et al.,[70] UK	591 (intervention outside hospital)	TIA and minor stroke that do not require immediate admission to hospital	Before after study	2002-2004 vs. 2004-2007	Early versus delayed assessment and treatment	↓ length of stay (conditional on hospital admission) ↓ hospital costs (conditional on hospital admission)	+
Wilson et al.,[71] UK	179 (5 centers)	Ischemic and hemorrhagic stroke	RCT	2004-2007	Acute treatment with antihypertensive drugs (yes/no)	Neutral, 3 month direct cost	-
Tay-Teo et al.,[73] Australia	71 (two hospitals)	Ischemic and hemorrhagic stroke	RCT	2004	Very early mobilization vs. standard care	↓ 3 and 12 month direct costs	-
Mar et al.,[72] Spain	304 (number not stated)	Ischemic stroke	Cohort	2000	Treatment with thrombolysis (yes/no)	↓ one-year direct cost	-
Moodie et al.,[68] Australian	395 (8 hospitals)	Ischemic and hemorrhagic stroke	Cohort	1999	Admission to stroke units vs. mobile services or general medical wards	Neutral, 28-week direct costs (comparison the both mobile service and medical ward)	-
Quaglini et al.,[66] Italy	351 (4 neurological ward)	Ischemic stroke	Cohort	1998-1999	Compliance vs. non-compliance with stroke guidelines	↓ hospital costs	+
Patel et al.,[67] UK	457 (3 care models)	Ischemic and hemorrhagic stroke	RCT	1995-1999	Admission to stroke units vs. stroke team or domiciliary care	Neutral, one-year direct costs (comparison with stroke team) ↑ one-year direct costs (comparison with domiciliary care)	-

Claesson et al.,[69] Sweden	249 (5 wards)	Ischemic and hemorrhagic stroke	RCT	1993-1994	Admission to stroke units vs. general medical ward	Neural, one-year direct cost	-

1.3.4. Medical specialization, processes of care, and outcome

For nearly two centuries, medical care has progressively been specialized in separate medical disciplines despite a recognition that specialization may lead to fragmentation of care.[46] The treatment and care of patients with stroke span multiple medical disciplines, including neurology, vascular medicine, internal medicine, and rehabilitation medicine, and it has been widely debated who should treat patients with stroke.[75] As a consequence, specialized stroke units are established in a variety of medical departments such as departments of geriatric medicine, general medicine, neurology, and rehabilitation medicine.[27, 76] There is an apparent positive benefit of stroke unit care across the different medical settings, but evidence suggests a trend towards a more disease-specific approach within stroke units located in departments of general medicine and neurology and a more generic disability approach in stroke units located within departments of geriatric medicine and rehabilitation medicine.[27] In Denmark, stroke care is increasingly centralized in neurological departments, but a considerable number of patients with stroke are still hospitalized in non-neurological medical settings.[76] Table 2 summarizes the relevant literature on the importance of medical specialization in stroke care.

The literature search found 14 relevant studies, but only one of the identified studies focused specifically on stroke unit care. The study is an Italian follow-up study of 11,572 acute stroke patients, which showed no difference in the risk of death or disability whether or not stroke units had only neurological beds (odds ratio (OR) 0.88, 95% confidence interval (CI) 0.55-1.39).[77] However, the risk of death or disability was reduced in patients who were admitted to conventional wards with only neurological beds (OR 0.64, 95% CI 0.55-0.75). A stroke unit was defined as a hospital ward with beds dedicated to stroke patients (at least 80% of stroke admissions) and dedicated staff who worked exclusively with stroke, whereas a conventional ward was defined as a hospital service in which stroke patients were cared for together with other patients and with neither beds nor staff dedicated to stroke patients alone. The remaining studies were not restricted to stroke units. In general, these studies confirm that patients with stroke benefit from neurological specialized care in terms of better survival,[77, 78, 78-82] reduced disability,[77, 80, 83] and reduced risk of readmissions[78, 84].

However, there are some indications that patients with concurrent diseases, in particular with symptoms of atherosclerotic heart disease, may not be treated optimally in neurological settings. Petty et al.[82] showed that patients with atrial fibrillation had worse survival when cared for on neurology services compared with general services, whereas patients without atrial fibrillation had better survival when cared for on neurology services. Furthermore, Schmith et al.[78] observed that collaborative care by generalists and neurologists was associated with better survival compared with care by neurologists alone, and that patients only cared for by neurologists had higher risk of readmissions with heart disease. The evidence regarding differences in resource utilization between neurological and non-neurological based stroke care is conflicting and inconclusive.[78, 80, 81, 83, 85] However, studies suggest that patients seen by neurologists are more likely than those not seen by neurologists to receive diagnostic testing, in particular MRI scan, and secondary medical prophylaxis, including ticlopidine, warfarin, heparin, and heparinoid.[78, 81, 83, 85, 86] Furthermore, neurologist involvement in stroke care has been linked with a higher overall compliance with process indicators regarding thrombolytic treatment, secondary medical prophylaxis, deep venous thrombosis prophylaxis, lipid testing, dysphagia screening, and smoking cessation.

In conclusion, the available evidence in general suggests that patients with stroke, who are not cared for in specialized stroke units, benefit from neurological specialized care. However, there are some indications that patients with concurrent diseases may not be treated optimally in neurological settings. Furthermore, the evidence suggests that patients receive increased diagnostic testing and secondary medical prophylaxis when cared for by neurologists compared with other specialists. No systematic differences in results were found between studies focusing on physician specialty and studies focusing on the medical specialty in departments.

Limitations of the existing studies: The majority of the existing studies were based on data more than 10 years old. However, modern stroke services are increasingly characterized by stroke dedication, continuous stroke training, and multidisciplinarity.[35] Therefore, a key question is whether the intensified stroke specialization in modern stroke care diminishes the basic differences between the primary medical specialities.[75] Furthermore, the existing studies had several methodological shortcomings. Most of the available evidence was based on observational studies and lacked control for potential important confounding factors, in particular initial stroke severity which is known to have major influence on stroke prognosis and health care costs.[87, 88] In addition, a number of studies did not take missing data[77-83, 85, 86, 88-91] and clustering (i.e. dependence) of patient outcome within providers or institutions into account.[79-82, 86, 88] Finally, the relationship between medical specialization and fulfillment of specific process criteria for a range of recommended, evidence-based processes of care remains virtually unexplored. In conclusion, it is unclear whether the perceived benefit of neurological specialization in stroke care can be found in modern stroke care.

Table 2. Summary of existing studies: medical specialization, processes of care, and outcome in patients with stroke (ordered by the year of follow-up)

Author, country	n, patients (institution)	Population	Study design	Follow-up	Medical specialization	Main findings	Adjustment for stroke severity
Saposnik et al.,[88] Canada	3756 (number not stated)	Ischemic stroke	Cohort	2003-2005	Neurologist vs. non-neurologist as most responsible physician	Neutral, mortality	+
Candelise et al.,[77] Italy	11572 (31 stroke units & 393 conventional wards)	Hemorrhagic and ischemic stroke	Cohort	2001	Stroke unit setting/conventional wards: all neurological beds (yes/no)	Stroke units: neutral (death or disability) Conventional wards: ↓ death or disability	Proxy measure
Reeves et al.,[91] USA	4897 (96 hospitals)	Ischemic stroke	Cohort	2001-2002	Neurologist involved in care (yes vs. no)	↑overall compliance with process indicators	-
Tseng et al.,[84] Taiwan	515 (number not stated)	Hemorrhagic and ischemic stroke		2000	Neurologist/neurosurgeon vs. non-neurologist as admitting physician	↓readmission	-
Smith et al.,[78] USA	44099 (11 metropolitan regions)	Ischaemic stroke	Cohort	1998-2000	Seen by a neurologist vs. non-neurologist during index hospitalization	↑warfarin ↓ mortality ↓ rehospitalization for infections and aspiration pneumonitis ↑ rehospitalization for atherosclerotic disease ↑ length of stay	-
Birbeck et	61541 (257	Hemorrhagic and	Cohort	1998-1999	Hospitals with or without a neurologist with specialty	Neutral, mortality	-

al.,[89] USA	hospitals)	ischemic stroke			training in stroke		
Gillum et al.,[80] USA	26925 (113 hospitals)	Ischemic stroke	Cohort	1997-1999	Neurologist vs. non-neurologist as attending physician	Neutral, mortality	-
Gillum et al.,[79] USA	10880 (29 hospitals)	Ischemic stroke	Cohort	1997-1999	Hospitals with vs. without a vascular neurologist	↓ mortality ↓ length of stay	-
Goldstein et al.,[85] USA	775 (9 hospitals)	Ischemic stroke	Cohort	1995-1997	Neurology service vs. non-neurology service	↑diagnostic testing ↑Ticlopidine, speech & occupational therapy ↓ mortality & disability Neutral, length of stay	+
Smith et al.,[92] USA	2320 (number not stated)	Hemorrhagic and ischemic stroke	Cohort	1991-1993	Admission to neurology wards vs. non-neurology wards	↓ mortality	+
Mitchell et al.,[81] USA	38612 (number not stated)	Ischemic stroke	Cohort	1991	Neurologist vs. non-neurologist as attending physician	↑diagnostic testing ↑ warfarin ↓ mortality ↑ 90-day cost	-
Horner et al.,[86] USA	146 (3 hospitals)	Ischemic stroke	Cohort	1987-1989	Admission to neurology/neurosurgery vs. non-neurology services	↑ diagnostic testing ↑ heparin or heparinoid	Proxy measure

						Neutral (mortality & functional status)	
Kaste et al.,[83] Finland	232 (6 departments)	Hemorrhagic and ischemic stroke	RCT	1987-1989	Admission to neurological vs. non-neurological department	↑ diagnostic testing Neutral, mortality & recurrent stroke ↑ discharge to home & functional status ↓ length of stay	+
Petty et al.,[82] USA	299 (number not stated)	Ischemic stroke	Cohort	1985-1989	Admission to neurology vs. non-neurology services	↑ carotid endarterectomy within 6 month ↓ mortality (patient without atrial fibrillation) ↑ mortality (patient with atrial fibrillation) Neutral, stroke recurrence	Proxy measure

1.3.5. Volume, processes of care, and outcome

Over the past decade, health care planning has increasingly aimed at concentrating health services based on the belief that larger units lead to reduced costs due to economies of scale and that larger units lead to improved patient outcome by increasing volumes of activity by clinicians.[93] Hospitals, and in particular small-scale hospitals, may experience economies of scale and thereby obtain reduced average costs per patient as volume increases.[93-95] However, the scale effect may diminish or even reverse (diseconomies of scale) in large-scale institutions; possibly due to deficient coordination, increased bureaucracy, and use of expensive technology due to specialization.[93-95] Higher volume of health services has also been linked with improved clinical outcome, in particular in patients undergoing invasive procedures.[44] However, despite ample evidence of scale advantages and disadvantages, the studies are subject to a general critique, particularly for not assessing differences in patient case mix and health care performance between high and low volume providers.[44, 93] Table 3 summarizes the relevant evidence on scale effects in stroke care.

Fourteen relevant studies were found by literature search, but only one of the identified studies was specifically restricted to stroke units. This study observed no difference in death or disability between patients who were admitted to stroke units treating more or less than 100 patients per year.[77] The remaining studies were not specifically restricted to stroke units and focused on volume, i.e. the number of patients treated, by physicians or institutions. Two studies focused on hospital size with regard to the number of hospital beds.[91, 96] The majority of the studies showed that higher stroke case volume was associated with reduced mortality,[88, 90, 97-102] and none of the studies observed a statistically significant association between higher volume and worse outcome.[77, 103, 104] One study focused on costs and showed that patients treated by physicians with high case volume incurred lower average inpatient costs compared with patients who were treated by low-volume physicians (on average 41% lower).[90] The costs were an aggregate of all itemized costs for services and disposables billed to the National Health Insurance. Length of stay was described as a key mediating variable in inpatient costs. With reference to health care performance, a larger number of hospital beds has been linked with receiving more processes of care, including thrombolytic treatment, secondary medical prophylaxis, deep venous thrombosis prophylaxis, lipid testing, dysphagia screening, and smoking cessation. The proportion of received processes of care by the smallest hospitals (<145 beds) was 11% lower than in the largest hospitals (>500 beds).[91] However, another study found no association between hospital size (17 hospitals included) and receiving specific processes of care, including thrombolytic therapy, dysphagia screening, prophylaxis for deep vein thrombosis, secondary medical prophylaxis, etiology documentation, smoke counseling, and stroke education.[96]

In conclusion, the available evidence either shows null-results or suggests that higher case volume is associated with receiving more processes of care, improved clinical outcome, and reduced costs. No systematic differences in results were found between studies focusing on volume by physicians or institutions.

Limitations of the existing studies: Specialization of personnel and equipment, improved clinical skills, and standardization of treatment are believed to be some of the mechanisms that may explain the act of economies of scale, and these features are also inherent characteristics of specialized stroke unit care.[54, 55] It is thus uncertain whether the scale advantages from treating a large number of patients exist in this setting.[77] Furthermore, the existing studies primarily addressed the importance of volume by hospitals or physicians, which reinforces the need for studies on the department/unit level because modern stroke care is increasingly characterized by dedicated departments/units with multidisciplinary team care.[35] The main limitations of the existing studies are insufficient control for potential confounders, in particular stroke severity,[90, 97-101] and limited evidence on differences in health care performance between high- and low-volume providers.[91, 96]Finally, the majority of studies relied on data from administrative databases,[90, 97-101, 104] but did not handle missing data with appropriate statistical methods although missing data are known to be common in observational research. [77, 88, 90, 91, 96-99, 101-105] In conclusion, it is unclear whether the scale advantages from treating a large number of patients exist in a specialized stroke unit setting and in particular, whether there are any differences in health care performance between high- and low-volume providers.

Table 3. Summary of existing studies: volume, processes of care, and outcome in patients with stroke (ordered by the year of follow-up)

Author, country	n, patients (institution)	Population	Study design	Follow -up	Volume (scale/categories)	Main findings (high vs. low volume)	Adjustment for stroke severity
Tung et al.,[100] Taiwan	258167 (number not specified)	Ischemic stroke	Cohort	1998-2007	Stroke patients/physician & stroke patients/hospital & hospital bed size (continuous)	↓ mortality (physician volume, stronger relationship in high-volume hospitals) Neutral, hospital volume and bed size (mortality)	-
Tung et al.,[101] Taiwan	34347 (2424 physicians, 245 hospitals)	Ischemic stroke	Cohort	2005	Stroke patients/physician & hospital volume (continuous)	↓ mortality (physician volume, stronger relationship in high-volume hospitals)	-
Saposnik et al.,[88] Canada	3756 (11 stroke centers)	Ischemic stroke	Cohort	2003-2005	Stroke patients/physician (continuous)	↓ mortality	+
Lin et al.,[90] Taiwan	83748 (number not stated)	Ischemic and hemorrhagic stroke	Cohort	2004	Stroke patients/physician (three equal groups (1-44, 45-135, ≥136))	↓ cost	-
Saposnik et al.,[98] Canada	26676 (606 hospitals)	Ischemic stroke	Cohort	2003-2004	Stroke patients/hospital (quartiles (1-62, 63-141, 142-197, ≥ 198) and categories (<50, 50-99, 100-199, ≥200)	↓ mortality	-
Saposnik et al.,[99] Canada	25228 (606 hospitals)	Ischemic stroke	Cohort	2003-2004	Stroke patients/hospital (50th percentile: 1-141, ≥142)	↓ mortality (high-income/high-volume group)	-
Ogbu et al.,[97] Netherlands	73077 (114 hospitals)	Ischemic and hemorrhagic stroke	Cohort	2000-2004	Stroke patients/hospital (quartiles (<162, 162-249, 250-353, >353) and cut-offs based on 3 previous publications)	↓ mortality	-

Reeves et al.,[91] USA	4897 (96 hospitals)	Ischemic stroke	Cohort	2001-2002	Hospital bed size (quartiles (27-145, 146-263, 264-499, 500-970))	↑overall compliance with process indicators	-
Hinchey et al.,[96] USA	2294 (17 hospitals)	Ischemic stroke	Cohort	2001-2002	Hospital size (not further defined)	Neutral, compliance with process indicators	-
Candelise et al.,[77] Italy	11572 (31 stroke units & 393 conventional wards)	Hemorrhagic and ischemic stroke	Cohort	2001	Stroke unit setting/conventional wards: patients/ward (0-100, >100)	Neutral in stroke units and conventional wards, death or disability	Proxy measure
Heuschmann et al.,[103] Germany	13440 (104 hospitals)	Ischemic stroke	Cohort	2000	Stroke patients/hospital (a priori analysis of cutoff points (0-249, >249))	Neutral, mortality	+
Reed et al.,[104] USA	23058 (137 hospitals)	Ischemic stroke	Cohort	1998-1999	Stroke patients/hospital (three categories (<100, 100-299, ≥300)	Neutral, receipt of IV tPA and mortality	Proxy measure
Votruba et al.,[102] USA	12150 (29 hospitals)	Ischemic and hemorrhagic stroke	Cohort	1991-1997	Stroke patients/hospital (continuous)	↓ mortality	Proxy measure

2. AIMS & HYPOTHESES

The main purpose of the thesis is to identify overall links in the relationships between selected aspects of specialization, processes of early stroke care, mortality, and hospital bed-day use among patients with stroke based on four epidemiological studies. Study I and II aim at identifying whether compliance with key recommendations for the early management of patients with stroke is associated with the length of hospital stay and hospital costs. Study III and IV aim at identifying whether selected aspects of specialization, including stroke unit setting (neurological or non-neurological) and case volume, is associated with compliance with key recommendations for the early management of patients with stroke, mortality, and hospital bed-day use. The studies are based on the following hypotheses:

1. Receiving evidence-based processes of care in the early phase of stroke is associated with shorter length of hospital stay and reduced hospital costs among patients with stroke (study I and II).

   Paper 1: ML Svendsen, LH Ehlers, G Andersen, SP Johnsen. Quality of Care and Length of Hospital Stay Among Patients With Stroke. Med Care. 2009;47(5):575-82.

   Paper 2: ML Svendsen, LH Ehlers, Hundborg HH, Ingeman A, Johnsen S. Quality of early stroke care and hospital costs. In preparation.

2. Neurological compared with non-neurological stroke unit setting is associated with receiving more evidence-based processes of early stroke care, reduced mortality, reduced number of readmissions, and reduced length of hospital stay among patients with stroke. Stroke patients with comorbid disease benefit less than patients without comorbid disease from care in neurological stroke unit settings (study III).

Paper 3: ML Svendsen, LH Ehlers, Ingeman A, Johnsen S. Quality of Care and Patient Outcome in Stroke Units: Is Medical Specialty of Importance? Med Care. 2011;49(8):693-700.

3. Higher annual case volume in stroke units is associated with receiving more evidence-based processes of early stroke care, reduced mortality, and reduced hospital bed-day use among patients with stroke (study IV).

   Paper 4: ML Svendsen, LH Ehlers, Ingeman A, Johnsen S. Higher stroke unit volume associated with improved quality of early stroke care and reduced length of stay. Submitted.

3. MATERIAL AND METHODS

3.1. DATA SOURCES

The studies in this thesis relied on data from Danish population-based medical registries,[106] including the Danish National Indicator Project,[7] the National Registry of Patients,[107] the Civil Registration System,[108] and the classification of Danish Hospitals and Departments.[109] Data in all registries were collected prospectively and independently of the thesis. 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 between databases.[108] The Danish health care system provides tax financed health care for all inhabitants of Denmark, including free access to hospital care.[110] All medical emergencies, including stroke, are exclusively admitted to public hospitals.[110]

In addition to the registries, we applied local hospital charges to estimate the costs of in-hospital care (study II).

3.1.1. The Danish National Indicator Project

All four studies used data from the Danish National Indicator Project. The Danish National Indicator Project was established in 2000 with the aim of documenting and improving the quality of care at a national level for selected diseases/conditions with a high incidence, mortality and/or high financial costs for the Danish hospital service.[111] The diseases/conditions include stroke, births, acute surgery of bleeding gastroduodenal ulcer and perforated peptic ulcer, chronic obstructive pulmonary disease, diabetes, heart failure, hip fracture, lung cancer, schizophrenia, and depression.[111] Participation is mandatory for all hospitals and departments treating patients with the specific diseases/conditions. As part of the Danish National Indicator Project, evidence-based disease-specific quality of care indicators have been developed relating to the structure, process, and outcome of care for each disease/condition, and prognostic factors have also been identified. The project includes prospective data collection, data analysis, evaluation and interpretation, feedback to providers and managers, clinical audit, implementation of quality improvement, and public release of all data. To ensure data quality and completeness, nationwide implementation pilot studies were carried out for each specific disease/condition, the inter-rater reliability has been examined by record review of randomly selected medical records, and the completeness of patient registration is continuously evaluated by comparison with local hospital discharge registries.[7, 111]

The DNIP-stroke registry includes data on compliance with key recommendations for the early management of patients with stroke[50, 112] and prognostic factors such as age, gender, smoking habits, alcohol consumption, Scandinavian Stroke Scale (SSS) score, atrial fibrillation, and hypertension. Data are collected prospectively upon hospital admission as part of daily clinical work by the health care professionals taking care of the patients. Detailed written instructions are available to ensure the validity of the data and the completeness of patient registration.[113] Data are transmitted securely via the Internet to the national DNIP-stroke database.

3.1.2. The National Registry of Patients

All four studies used data from the National Registry of Patients.[107] This registry primarily aims at monitoring health care utilization and supporting health care planning. The registry is increasingly used for medical research and quality assurance as well. The registry covers all somatic hospital admissions since 1977, and outpatients and emergency room patients since 1995, and registration is mandatory. Data are registered on discharge diagnoses and service dates (e.g. dates of admission and discharge for inpatients, and dates of visit for emergency room patients) from each hospital contact through life. The diagnoses were coded according to the 8th edition of the International Classification of Diseases (ICD-10) from 1977 to 1993, and according to the 10th edition (ICD-10) since 1994.

3.1.3. The Civil Registration System

All four studies used data from the Civil Registration System. The purpose of the Civil Registration System is to administrate the personal identification number system. Since 1968, all Danish residents have been assigned a unique 10-digit personal identification number at birth or immigration. The number is used in all public registries and enables unambiguous record linkage between databases. Among other variables, the Civil Registration System contains data on name, date of birth, place of residence, and vital status (updated on a daily basis). The validity of the recorded information is considered to be very high since registration is mandatory by law and the information is extensively used for administrative purposes.[108]

3.1.4. The Classification of Danish Hospitals and Departments

Study II, III, and IV used data from the Classification of Danish Hospitals and Departments. This registry is used to identify the service provider in reporting to the National Registry of Patients. The registry uniquely identifies all Danish hospitals, hospital departments, and hospital units, and includes information on the primary medical specialty of each department/unit.[109] All Danish hospitals report changes in hospital organization to the

National Board of Health, and the information is continuously updated on the board´s official webpage (http://www.medinfo.dk/sks/brows.php).

3.1.5. Local hospital charges

In study II, local charges from the former Aarhus County Hospital and the Hammel Neurorehabilitation Centre were applied to estimate the daily average costs of in-patient care in different medical facilities.

3.2. STUDY DESIGN AND STUDY POPULATION

All four studies were designed as population-based cohort studies. Study I and II covered the former Aarhus County, whereas study III and IV were nationwide. The study periods were: January 2003-November 2005 (study I), January 2005-December 2010 (study II), January 2003-December 2007 (study III), and January 2003-December 2009 (study IV).

In all four studies, the study population was identified through the DNIP-stroke database and included patients with acute stroke who were admitted to specialized stroke units in Denmark. The DNIP-stroke database includes patients (≥18 years) that are hospitalized with acute stroke according to the WHO criteria, i.e. rapidly developing symptoms and signs of focal or global neurological dysfunction of presumed vascular etiology lasting more than 24 hours or leading to death.[8] Patients with intracerebral haemorrhage and ischemic stroke are included (ICD-10: I63, infarction; I61, haemorrhage; and I64, unspecified).[114] Patients with subarachnoid or epidural hemorrhage, subdural hematoma, retinal infarct, and infarct caused by trauma, infection, or an intracranial malignant process are excluded. Patients with diffuse symptoms, such as isolated vertigo or headache, and asymptomatic patients with infarct detected only by CT or MRI scan are also excluded. In the Danish National Indicator Project, a stroke unit is classified as a hospital department or unit exclusively or primarily dedicated to patients with stroke and characterized by multidisciplinary teams, staff with specific interest in stroke, involvement of relatives, and continuous education of the staff. The health care professionals taking care of the patients must specifically check in the registration form whether the patient was admitted to a stroke unit and the date of admission.[115] Although some patients had multiple events during the study period, we included only the first stroke event registered in the DNIP-stroke database in order to ensure independence between observations. Furthermore, only patients with a valid civil registration number were included.

In all four studies, follow-up began on the day of hospital admission with stroke, and the patient´s exposure status was classified according to the timeliness of provided care (study I and II), the stroke unit setting (neurological vs. non-neurological; study III), and the annual case volume in stroke units (study IV). The end of follow-up depended on the outcomes.

3.3. DEFINITIONS OF VARIABLES

3.3.1. Processes of early stroke care

In study I and II, the processes of care were assessed as the independent variable (i.e. the exposure), whereas the care processes were examined as possible mediators of the association between stroke unit setting and outcome in study III and annual case volume and outcome in study IV. Data on the processes of care were obtained from the DNIP-stroke registry.

As part of the Danish National Indicator Project, the processes of care covering the early phase of stroke were identified by a national expert panel of physicians, nurses, physiotherapist, and occupational therapists, taking into account the strength of evidence, the feasibility of collecting the required data in routine clinical settings, and the ability of the processes to reflect the multidisciplinary efforts involved in modern stroke care.[7, 116] The processes of care agree with international consensus guidelines for the early management of patients with stroke.[50, 112] A time limit was defined for each process to capture the timeliness of care (Table 4). Furthermore, patients were classified as eligible or ineligible for the individual processes of care depending on whether the stroke team identified contraindications, such as gastrointestinal bleeding precluding early antiplatelet therapy and rapid spontaneous recovery of motor symptoms making early assessment by a physiotherapist irrelevant. In the four studies in this thesis, only eligible patients were included in the analyses. Study III and IV included seven processes of care registered on a national basis, whereas study I and II included an additional five processes of care that were only registered in Aarhus County. In all four studies, an overall percentage score was calculated to reflect the overall quality of early stroke care. The score was calculated by dividing the total number of received processes of care within the time limit for each patient with the total number of processes of care that the patient was eligible for.

Table 4. Definitions of the processes of early stroke care

Processes of care*	Definition	Time limit
Admission to a specialized stroke unit	Admission to a hospital department/unit exclusively or primarily dedicated to patients with stroke and characterized by multidisciplinary teams, a staff with a specific interest in stroke, involvement of relatives, and continuous education of the staff	Second day of hospitalization
Antiplatelet therapy initiated among patients with ischemic stroke without atrial fibrillation, or oral anticoagulant therapy initiated among patients with ischemic stroke and atrial fibrillation	Continuous use of the drugs and not merely a single dose	Antiplatelet therapy on second day of hospitalization or oral anticoagulant therapy on 14th day of hospitalization
CT/MRI scan		First day of hospitalization (second day in study I)
Assessment by a physiotherapist and occupational therapist	Formal bed-side assessment of the patient's need for rehabilitation	Second day of hospitalization
Nutritional risk assessment	Assessment following the recommendations of the European Society for Parenteral and Enteral Nutrition[117]	Second day of hospitalization
Assessment of swallowing function	Assessment according to the Gugging Swallowing Screen[118]	First day of hospitalization (second day in study I)
Assessment of constipation risk	Assessment upon admission by anamnesis	Second day of hospitalization
Early mobilization	Out-of-bed mobilization of the patient to a sitting position, standing or walking (unassisted or assisted), depending on the patient's general condition.	First day of hospitalization (second day in study I)
Intermittent catheterization	Treatment with sterile intermittent catheterization	Second day of hospitalization
Thromboembolism prophylaxis	Venous thromboprophylaxis with compression stockings and/or low molecular weight heparin (compression stockings only until 2006)	Second day of hospitalization

* All processes of care must be documented in the patient record

3.3.2. Medical setting and volume

Study III examined the stroke unit setting as the independent variable; i.e. the exposure. Stroke unit setting refers to the medical department in which the stroke unit was established. Stroke unit setting was classified according to the official Danish Classification of Danish Hospitals and Departments which uniquely identifies all Danish hospital departments/units and the primary medical specialty of each department/unit.[109] Stroke units in neurological settings were all located within departments of neurology, some of them also including neurosurgery and neurophysiology. Stroke units in non-neurological settings were located within departments of internal medicine, geriatrics, cardiology, hematology, nephrology, gastroenterology, endocrinology, oncology, respiratory medicine, infectious medicine, or rheumatology. Stroke units located in neurological settings were all served by neurologists whereas the stroke units in non-neurological settings were served by other specialists.

Study IV examined the annual case volume in stroke units as the independent variable; i.e. the exposure. Data were obtained from the DNIP-stroke database. Annual case volume included the total number of stroke patients treated in an individual stroke unit per year and was calculated by averaging whole-year registrations in the study period including all stroke admissions irrespective of whether the patient died during hospitalization or was readmitted.

3.3.3. Mortality and readmissions

In study III and IV, follow-up regarding mortality began on the day of hospital admission and continued until 30 days or one year after admission. Data on mortality were obtained from the Civil Registration System. In study III, any acute readmission with overnight stay (all causes) by 30-days after hospital discharge was considered a readmission. Data were obtained from the National Registry of Patients.

3.3.4. Length of hospital stay and hospital costs

In all four studies, the length of hospital stay was defined as the time span from hospital admission, or stroke occurrence if already hospitalized, until death or discharge. Data on length of hospital stay was obtained from the DNIP-stroke registry. Study III and IV were nationwide and included both acute stroke units and comprehensive stroke units (i.e. units covering both the acute phase and the rehabilitation phase), and some inherent variation in length of hospital stay between the departments should therefore be expected. In study I and II, the length of hospital stay included the acute hospitalization and inpatient rehabilitation for all patients. One-year bed-day use (study IV) included every hospitalization with at least one overnight stay for all causes during the first year after admission with stroke. The information was obtained from the National Registry of Patients.

In study II, the calculation of hospital costs was made individually for each patient from the hospital perspective. The calculation was based on daily hospital charges for days spent in an intensive care unit (ICU), acute care and in-patient rehabilitation, which studies have identified as main predictors of the total costs of in-hospital care.[26, 28, 29, 119] The information on bed-day use was obtained from the Danish National Indicator Project and the National Registry of Patients. The costs were estimated by multiplying the bed-days in each facility (i.e. ICU, acute care, and rehabilitation) by local hospital charges for 2010 from the former Aarhus County Hospital and the Hammel Neurorehabilitation Centre. The daily charges were 4127 United States Dollar (USD) per day for ICU, 1534 USD per day for acute care, and 821 USD per day for in-hospital rehabilitation. The costs of providing the specific processes of care were not included in the cost calculation since nearly all patients received the processes of care at some time during hospitalization, but not necessarily in the early phase of stroke, and the costs were assumed to be practically identical irrespective of at what time during hospitalization the process was received (Table 5). In addition, the potential bed-day cost savings were estimated by multiplying the saved bed-days per person with a daily base charge for nonmedical services such as meals, cleaning, heating, water, and electricity (353 USD). All costs were converted into USD by applying the exchange rate on the 1st of January 2010 (1 DKK=0.193155 USD). We did not discount the costs because of the short time period analyzed.

3.3.5. Covariates

The DNIP-stroke database includes a number of key prognostic factors covering sociodemographic and clinical characteristics, all of which are associated with stroke mortality, disability, and/or costs.[115] These factors were included as covariates in the four studies of this thesis. In addition to these variables, adjustment was made for practice environment (stroke unit volume, stroke unit setting, hospital university status, and received processes of care) which is lacking in most prior research on the relationship between health care specialization and outcome.[43, 44] The available literature suggests that patients with chronic and comorbid diseases may profit less by specialized care.[43, 82, 95, 120] The Charlson comorbidity index was therefore used to adjust for comorbid disease and evaluate possible interactions in the association between stroke unit setting and outcome (study III) and stroke unit volume and outcome (study IV). The Charlson comorbidity index quantifies the severity of comorbid disease in a summary score based on the presence or absence of 19 medical conditions,[121] and it is a useful score to adjust for comorbid disease in stroke outcome studies.[122] We used an adapted version of the index that utilizes ICD codes by identifying discharge diagnoses for each patient from 1994 onwards in The Danish National Registry of Patients.[123] Recently, the positive predictive values of the diagnoses included in the Charlson comorbidity index, as ascertained in the National Registry of Patients, was found to be consistently high.[124]

3.4. STATISTICAL ANALYSIS

We included only the first stroke event registered in the DNIP-stroke database to guarantee independence between the observations. The characteristics of the study populations were described by percentages, means, standard deviations, medians, and quartiles.

We performed both unadjusted and adjusted analyses. The analyses were adjusted for a wide range of patient and service characteristics know to be associated with outcome in order to minimize possible confounding. Age and stroke severity are particularly important in relation to patient prognosis and hospital costs,[26, 32] and adjustment was made with natural cubic splines in order to perform a more complete confounder control for these factors (study II, III, and IV).[125] In study III (stroke unit setting) and IV (stroke unit volume), adjustment was made separately for patient characteristics, hospital- and unit characteristics, and processes of early stroke care in order to segregate their possible impact on the studied associations. The Wald test was used to test whether the results differed between strata of age, severity of comorbid disease, and initial disease severity. The statistical significance level was 0.05 in all studies. Data were analyzed using Stata (StataCorp LP, College Station, TX) (version 9.2 in study I, and version 10 in study II, III, and IV).

The applied categorizations of volume may affect the observed relationship between volume and mortality among patients with stroke, although there seems to be a consistent survival benefit in high-volume hospitals compared with low-volume hospitals.[97] Therefore, it was specified a priori that the analyses in study IV should be performed by volume quartiles of approximately equal number of patients; i.e. 0-231 patients/year (low-volume), 232-330 (low/medium-volume), 331-498 (medium/high-volume), and 499-915 (high-volume), in accordance with several previous studies.[91, 97, 98] Figure 2 shows that there were no essential non-linear relationships between volume and the outcomes.

3.4.1. Linear regression

We used linear regression to analyze the linear outcomes, i.e. the percentage score for overall quality of care (study III and IV), length of hospital stay (all studies), hospital costs (study II), and one-year bed-day use (study IV). The percentage score for overall quality of care was analyzed on the original scale and the results were expressed as absolute differences in percentage points. Length of hospital stay, one-year bed-day use, and hospital costs were analyzed on the logarithmic scale as the data distributions were positively screwed. When reporting the final results, the estimates were transformed back into the original units by exponentiating the estimates, and the results were expressed as ratios of the geometric means of length of hospital stay, one-year bed-day use, and costs.[126]

3.4.2. Logistic regression

We used logistic regression to estimate the OR of the binary outcomes, i.e. the individual processes of care (study III, IV), 30-day and one-year mortality (study III, IV), and 30-day readmission (study III). The results were expressed as OR, i.e. the odds of outcome in exposed groups compared with odds of outcome in unexposed groups. The OR for 30-day mortality and 30-day readmission approximate the risk ratio (RR) because these outcomes were relatively rare (≈10%).[127]

3.4.3. Cluster within departments

Data are clustered if observations in one cluster tend to be more similar to each other than to individuals in the rest of the sample.[128] If the presence of clustering is not accounted for in the statistical analyses, the standard errors may be too small and the confidence intervals too narrow. In all four studies, the results were corrected for clustering of patients within stroke units, taking into account unmeasured characteristics of the stroke units that may be associated with outcome. The applied statistical techniques were random effect modeling (study I) and robust estimates of the variance derived from the Huber/White/sandwich estimator of variance (study II, III, and IV).[128]

3.4.4. Missing data

For up to 40% of the patients, information was missing on at least one of the covariates. The risk of bias from missing data depends on the reasons why data are missing.[129] Analyzing cases with complete information produces valid estimates only when data are missing completely at random; i.e. if subjects with missing data are a random subset of the complete sample of subjects. In most cases, the probability that an observation is missing depends on other observed patient characteristics, and data are described as missing at random.[130] In this case, complete case analysis most likely suffers from selection bias. There are several methods available for handling missing data, including multiple imputation of missing values which is believed to give sound results with respect to both bias and precision.[129] Multiple imputation was therefore used to impute missing values in study II, III, and VI. The basic steps in multiple imputation is to create several imputed datasets (missing values are predicted from the remaining, known characteristics), analyze each imputed dataset with standard analytical techniques, and average the estimates to get a pooled estimate of the association taking into account both sampling and imputation uncertainty.[129, 130] In study I, we created an extra category for missing data (the missing-indicator method). The inclusion of all subjects in the multivariable analysis is the main advantage of this method, but results may be subjected to bias and erroneous small standard errors.[129, 130]

3.4.5. Sensitivity analysis

The aim of a sensitivity analysis is to evaluate how sensitive the main results are to changes in the analysis strategies or assumptions. It is made by systematically repeating the statistical analysis using different strategies or assumptions each time.[105, 131] The robustness of the results presented in this thesis was evaluated in several sensitivity analyses. Among others, a complete case analysis was performed in order to assess the impact of missing data (all four studies). Furthermore, the analyses were repeated by strata of stroke severity, severity of comorbid disease, and/or age in order to evaluate possible interaction (study I, III, and IV). The analyses were also repeated including only patients who survived until hospital discharge in order to evaluate the impact of in-hospital death in shortening the length of hospital stay and reducing the costs (study I, II, and IV).

3.6. PERMISSIONS

Permissions to use and link public registries were obtained from the Danish Data Protection Agency, the Danish National Indicator Project, and the National Board of Health.

4. RESULTS

4.1. DESCRIPTIVE STATISTICS

The four studies in this thesis covered different study periods and geographical areas, but there were no major differences in the sociodemographic and clinical patient profile between the studies. Based on nationwide data from 2009, 67% of the patients were seen in stroke units established in neurological departments, and 58% of the patients were seen in high-volume stroke units. In general, patients in neurological stroke unit settings and high-volume stroke units had a more favorable prognostic profile compared with patients receiving care in less specialized stroke unit settings (study III and IV). These patients tended to be younger, have less atrial fibrillation and less hypertension, and less severe stroke upon hospital admission. The number of patients who received care in neurological stroke unit settings and high-volume stroke units increased during the study period.

Almost all patients, who were considered eligible for care, received the processes of care at some time during hospitalization, but not necessarily within the recommended time limit. Table 5 displays the performance of the processes of care for patients who were admitted to Danish stroke units during 2009.

Table 5. Processes of care (nationwide data from 2009)

Process (time limit)	Eligible patients, n	Received on time, %	Received during hospitalization, %	Missing data, %
Stroke unit (by day 2)	9536	94.3	100	0
Antiplatelet therapy (by day 2)	6328	88.5	97.6	2.3
Anticoagulant therapy (by day 14)	744	74.3	79.7	7.5
CT/MRI scan (by day 1)	9386	71.0	99.7	1.0
Physiotherapy (by day 2)	7700	75.2	98.8	2.5
Occupational therapy (by day 2)	7848	72.4	98.5	2.5
Nutritional assessment (by day 2)	7985	69.9	92.6	5.3

4.2. STUDY I & II: PROCESSES OF EARLY STROKE CARE

For study I (2003-2005) and II (2005-2010), we identified a total of 2,636 and 5,909 patients with stroke, respectively, who were admitted to dedicated stroke units in the former Aarhus County, Denmark. The studies showed that receiving evidence-based processes of early stroke care was associated with shorter length of hospital stay as well as reduced hospital costs (Table 6). The adjusted ratio of length of stay ranged from 0.67 (95% CI: 0.61-0.73) for early mobilization to 0.87 (95% CI: 0.81-0.93) for early physiotherapy assessment, and the adjusted ratio of hospital costs ranged from 0.65 (95% CI: 0.50-0.85) for early admission to a stroke unit to 0.97 (95% CI: 0.72-1.31) for early thromboembolism prophylaxis. The association between receiving more evidence-based processes of care in the early phase of stroke and the length of hospital stay and hospital costs seemed to follow an inverse dose-response pattern. According to study I, patients who received between 75% and 100% of the processes of care within the lime limit were hospitalized about half as long as patients who received between 0% and 25% (adjusted ratio of length of stay: 0.53, 95% CI: 0.48-0.59). In study II, the hospital costs were about 50% less among patient who received between 75% and 100% of the processes of care within the time limit compared with patients who received between 0% and 25% (adjusted ratio of hospital costs: 0.52, 95% CI: 0.39-0.70). The potential savings in bed-day costs were 4553 USD per patient (95% CI: 3980-5127) for patients who received 75-100% of the processes of care within the time limit compared with patients who received 0-24%.

The results were in general confirmed by all sensitivity analyses, including complete case analyses (both studies), analyses restricted to survivors (both studies), analyses without correction for cluster within stroke units (study I), analyses with adjustment for 19 specific comorbidities instead of adjustment for the Charlson comorbidity index (study I), analyses stratified by stroke subtype (study I), and analyses in which the hospital charges in each in-hospital facility (ICU, acute care, and rehabilitation) were varied by 50% (study II). Adjustment for medical complications during hospitalization (both studies) only had minor impact on the results.

Table 6. Processes of early stroke care, length of hospital stay, and hospital costs

Process of care	Length of stay		Hospital costs	
	n, yes/no	Adjusted ratio (95% CI)*	n, yes/no	Adjusted ratio (95% CI)*
Stroke unit by day 2	2055/581	0.65 (0.59-0.73)	5187/721	0.65 (0.50-0.85)
Antiplatelet therapy by day 2	1242/480	0.77 (0.68-0.86)	3285/464	0.77 (0.66-0.90)
Anticoagulant therapy by day 14	177/81	0.74 (0.57-0.98)	372/125	0.84 (0.55-1.30)
CT/MRI scan by day 2 / 1	2306/314	0.91 (0.80-1.04)	4456/1391	0.86 (0.72-1.02)
Physiotherapy by day 2	1093/1231	0.79 (0.72-0.87)	3646/1564	0.80 (0.73-0.87)
Occupational therapy by day 2	1032/1322	0.76 (0.70-0.83)	3604/1591	0.80 (0.74-0.87)
Nutritional assessment	969/1126	0.73 (0.66-0.81)	3866/1361	0.79 (0.69-0.91)
Swallowing assessment 2 / 1	1168/289	0.65 (0.56-0.76)	3235/1862	0.78 (0.69-0.88)
Constipation assessment by day 2	362/648	0.52 (0.46-0.59)	2752/1280	0.83 (0.72-0.96)
Mobilization by day 2 / 1	1662/487	0.42 (0.38-0.47)	2978/2274	0.70 (0.62-0.79)
Sterile catheterization by day 2	224/147	0.72 (0.58-0.90)	499/451	0.85 (0.56-1.31)
Thromboembolism prophylaxis by day 2	198/276	0.80 (0.66-0.96)	599/867	0.97 (0.72-1.31)

* The analyses were clustered within stroke units by random effect modeling (length of stay) or robust standard errors (hospital cost), and adjusted for age, gender, marital status, housing, profession, alcohol intake, smoking habits, Modified Rankin Scale Score prior to admission, atrial fibrillation (except for criteria on antiplatelet and anticoagulant therapy), hypertension, hyperlipidemia, Charlson comorbidity index, Scandinavian Stroke Scale score upon admission, type of stroke (except for criteria on antiplatelet and anticoagulant therapy), and year of hospitalization. The results from study I were further adjusted for transfer to a rehabilitation ward, and the results from study II were further adjusted for hospital university status, stroke unit volume, and treatment with thrombolysis.

4.3. STUDY III: MEDICAL SETTING

Study III included 45,521 patients with stroke who were admitted to 57 stroke units in Denmark during 2003 to 2007. 67% of the patients were admitted to stroke units located within departments of neurology, whereas the remaining 33% were admitted to stroke units located in a non-neurological setting (primarily department of internal medicine, geriatrics, and cardiology).

Patients in neurological stroke unit settings had higher odds of receiving early antiplatelet therapy (unadjusted OR 1.68, 95% CI: 1.10-2.56) and early CT or MRI scan (unadjusted OR 1.77, 95% CI: 1.29-2.45) compared with patients in non-neurological stroke unit settings. No other major differences were found in processes of care between neurological- and non-neurological stroke unit settings when evaluating early admission to a stroke unit, early anticoagulant therapy, early physiotherapy- and occupational therapy assessment, and early assessment of nutritional risk. The association between stroke unit setting and the processes of care was unrelated to the severity of comorbid disease, except for higher odds of CT or MRI scan among patients without comorbid disease in neurological stroke unit settings (Table 7).

There were no overall associations between stroke unit setting and the odds of death, readmissions, or length of hospital stay (see Table 4 in the corresponding publication). However, patients in neurological settings suffering from moderate comorbid disease had statistically significant increased odds for one-year mortality (adjusted OR 1.18, 95% CI: 1.02-1.36) compared with patients in non-neurological settings, but the associations between volume and mortality did not vary statistically significantly between patients with no, moderate, or severe comorbid disease. Adjustment for patient characteristics and hospital characteristics had some impact on the analyses on mortality and length of hospital stay, whereas the results remained virtually unchanged when adjustment was also made for the overall percentage score for quality of care. The results were confirmed by a complete case analysis.

Table 7. Stroke unit setting and processes of care according to comorbid disease

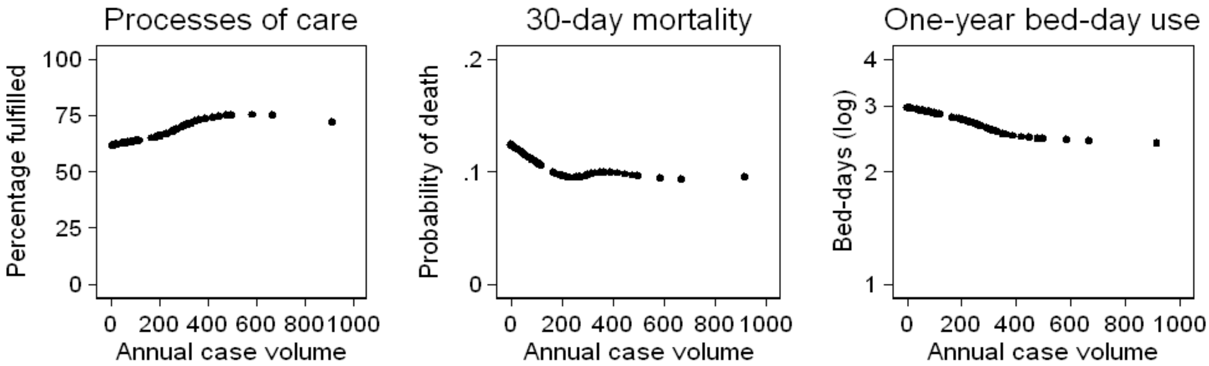
Process of care	Neurological setting	Eligible patients, n	Process received, %	Unadjusted odds ratio (95% CI)*	p-value
Stroke unit (by day 2)					
No comorbidity	Yes	9246	93.1	1.55 (0.86-2.78)	0.14
	No	5292	89.7	1	
Moderate comorbidity	Yes	14843	92.1	1.51 (0.85-2.67)	
	No	6885	88.6	1	
Severe comorbidity	Yes	6268	89.4	1.38 (0.77-2.46)	
	No	2987	86.0	1	
Antiplatelet therapy (by day 2)					
No comorbidity	Yes	6735	84.1	1.68 (1.06-2.66)	0.18
	No	3841	75.8	1	
Moderate comorbidity	Yes	8996	85.1	1.67 (1.12-2.49)	
	No	4296	77.4	1	
Severe comorbidity	Yes	3492	82.4	1.71 (1.08-2.69)	
	No	1739	73.3	1	
Anticoagulant therapy (by day 14)					
No comorbidity	Yes	509	61.1	0.71 (0.40-1.25)	0.60
	No	403	69.0	1	
Moderate comorbidity	Yes	1177	56.7	0.74 (0.45-1.23)	
	No	711	63.9	1	
Severe comorbidity	Yes	655	57.1	0.77 (0.48-1.25)	
	No	367	63.2	1	
CT/MRI-scan (by day 1)					
No comorbidity	Yes	9008	53.7	1.80 (1.27-2.53)	0.02
	No	5231	39.3	1	
Moderate comorbidity	Yes	14256	58.7	1.74 (1.25-2.44)	
	No	6747	44.9	1	
Severe comorbidity	Yes	6022	56.6	1.74 (1.28-2.38)	
	No	2913	42.8	1	
Physiotherapy (by day 2)					
No comorbidity	Yes	7169	61.7	0.91 (0.66-1.26)	0.11
	No	4773	63.8	1	
Moderate comorbidity	Yes	11747	59.5	0.86 (0.62-1.20)	
	No	6153	63.1	1	
Severe comorbidity	Yes	5023	58.7	0.96 (0.68-1.35)	
	No	2654	59.7	1	
Occupational therapy (by day 2)					
No comorbidity	Yes	7356	56.6	0.87 (0.67-1.15)	0.71
	No	4798	59.8	1	
Moderate comorbidity	Yes	11753	54.1	0.85 (0.65-1.11)	
	No	6067	58.2	1	
Severe comorbidity	Yes	4995	53.2	0.87 (0.67-1.14)	
	No	2646	56.5	1	
Nutritional assessment (by day 2)					
No comorbidity	Yes	6776	65.8	1.37 (0.99-1.89)	0.25
	No	4186	58.5	1	
Moderate comorbidity	Yes	10414	60.7	1.36 (0.97-1.89)	
	No	5299	53.3	1	
Severe comorbidity	Yes	4330	58.1	1.35 (0.94-1.95)	
	No	2311	50.6	1	

* 95% CIs were calculated using robust estimates of the variance that allowed for clustering of patients within stroke units.

4.4. STUDY IV: VOLUME

Study IV included 63,995 patients with stroke who were admitted to 61 stroke units in Denmark between 2003 and 2009. Spline curves showed no essential non-linearity in the relationships between volume, the percentage score for quality of care, and outcome (Figure 2).

Figure 2. Stroke unit volume, processes of care, and outcome (spline curves)



Patients who were admitted to high-volume stroke units received on average more processes of care in the early phase of stroke compared with patients in low-volume stroke units (499-915 vs. 0-231 patients/year: unadjusted difference in percentage points 9.84, 95% CI: 3.98-15.70). Patients had substantially higher odds of being admitted early to high-volume stroke units compared with low-volume stroke units (499-915 vs. 0-231 patients/year: unadjusted odds ratio 3.44, 95% CI: 1.69-7.00). Furthermore, patients in high-volume stroke units had statistically significantly higher odds of receiving early antiplatelet therapy, early CT/MRI scan, early occupational therapy assessment, and early nutritional assessment.

Higher case volume was consistently associated with shorter length of the initial hospital stay (499-915 vs. 0-231 patients/year: adjusted ratio 0.49, 95% CI: 0.41-0.59), as well as with reduced bed-day use in the first year after stroke when focusing on all-cause hospitalizations (499-915 vs. 0-231 patients/year: adjusted ratio 0.79, 95% CI: 0.70-0.87)

(Table 8). We found no statistically significant association between volume and 30-day or one-year mortality.

Adjustment for hospital characteristics and the overall percentage score for quality of care in addition to adjustment for patient characteristics had no major impact on the results. Furthermore, when stratifying the analyses according to the severity of comorbid disease, age, and initial stroke severity we did not find any indication of interaction. The results were in general confirmed by a complete case analysis and analyses including only survivors.

Table 8. Stroke unit volume and outcome

	n, patients	Events, %/ Median (IQR)*	Unadjusted ratio (95% CI)*	Adjusted ratio (95% CI)*†
30-day mortality				
Volume 0-231	14617	9.6	1	1
Volume 232-330	16784	10.0	1.04 (0.85-1.28)	1.09 (0.88-1.36)
Volume 331-498	16461	9.9	1.04 (0.84-1.28)	1.12 (0.91-1.38)
Volume 499-915	16133	9.4	0.98 (0.82-1.17)	1.10 (0.91-1.33)
One-year mortality				
Volume 0-231	14617	21.9	1	1
Volume 232-330	16784	21.9	1.00 (0.87-1.15)	1.07 (0.94-1.21)
Volume 331-498	16461	21.1	0.96 (0.81-1.13)	1.05 (0.92-1.21)
Volume 499-915	16133	19.9	0.89 (0.77-1.02)	1.03 (0.86-1.22)
Length of stay				
Volume 0-231	14617	12 (5-27)	1	1
Volume 232-330	16784	7 (4-16)	0.67 (0.50-0.89)	0.67 (0.55-0.82)
Volume 331-498	16461	6 (3-13)	0.55 (0.43-0.71)	0.57 (0.45-0.72)
Volume 499-915	16133	5 (3-9)	0.46 (0.32-0.65)	0.49 (0.41-0.59)
Bed-days/year				
Volume 0-231	14617	18 (8-40)	1	1
Volume 232-330	16784	15 (6-37)	0.83 (0.69-1.00)	0.89 (0.75-1.05)
Volume 331-498	16461	12 (4-34)	0.70 (0.61-0.82)	0.78 (0.69-0.89)
Volume 499-915	16133	11 (4-33)	0.68 (0.59-0.78)	0.79 (0.70-0.87)

* Percentage and odds ratio if mortality, and median (interquartile range) and ratio between geometric means otherwise.

† Adjusted for age, gender, marital status, housing, alcohol intake, smoking habits, Charlson comorbidity index, atrial fibrillation, hypertension, Scandinavian Stroke Scale score upon admission, stroke subtype, treatment with thrombolysis, calendar year, stroke unit setting, and hospital university status.

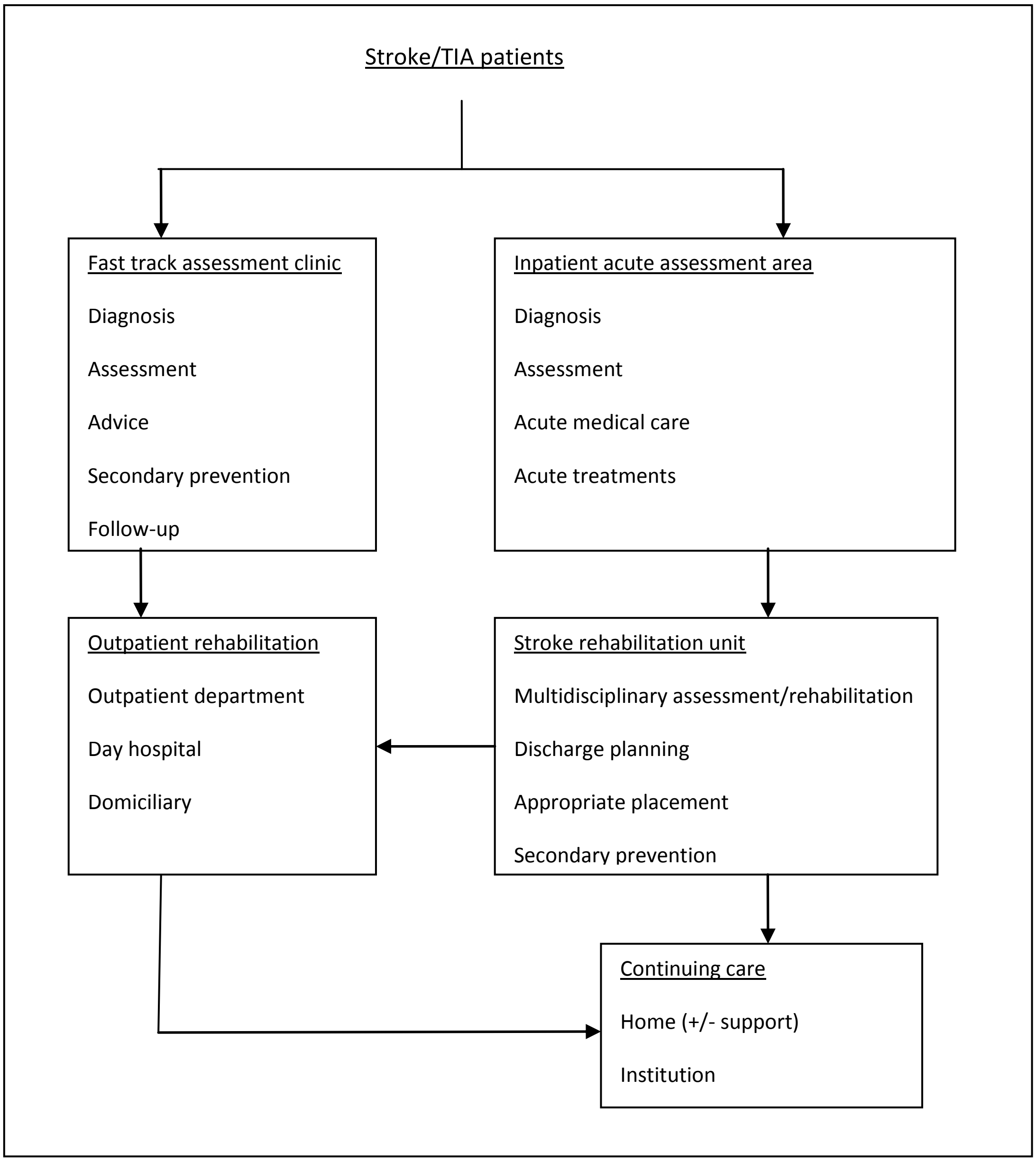
5. DISCUSSION

This thesis showed that early stroke care in agreement with key recommendations for the early management of patients with stroke may be associated with shorter length of hospital stay and potential savings in hospital costs. Furthermore, higher annual case volume in stroke units may be associated with higher quality of early stroke care and fewer days spent in hospital during the first year after stroke, whereas no association was observed between volume and mortality. Except for early CT or MRI scan and early antiplatelet therapy in neurological stroke unit settings, the medical setting of stroke units appeared not to be related to other essential processes of early stroke care and outcome.

5.1. STROKE SERVICE INTERVENTIONS

Comprehensive stroke services require a range of facilities as illustrated in figure 2. Stroke units constitute an important part of these services, but other elements in the continuum of care may also affect stroke prognosis such as the pre-hospital management of stroke.[27, 70, 132] The effect of service interventions may operate though several links to improve patient outcome; for example through clinical pathways and specific clinical interventions.[133] Furthermore, a disease or an outcome is usually caused by many factors, and an interplay of environment, behavior, and subcellular biology may act together in a causal pathway.[134] The causal interpretation is further challenged since associations between service interventions and outcome may be reversible which contradicts the traditional epidemiological view of a necessary one-way temporal relationship from cause to effect.[135] For example, an association between higher volume and shorter initial length of stay (study III) may originate from a reverse relationship because early discharge releases capacity for more patients. This illustrates the complexity of causation and underlines the need for paying special attention to whether the results in this thesis can be interpreted as causations or associations.

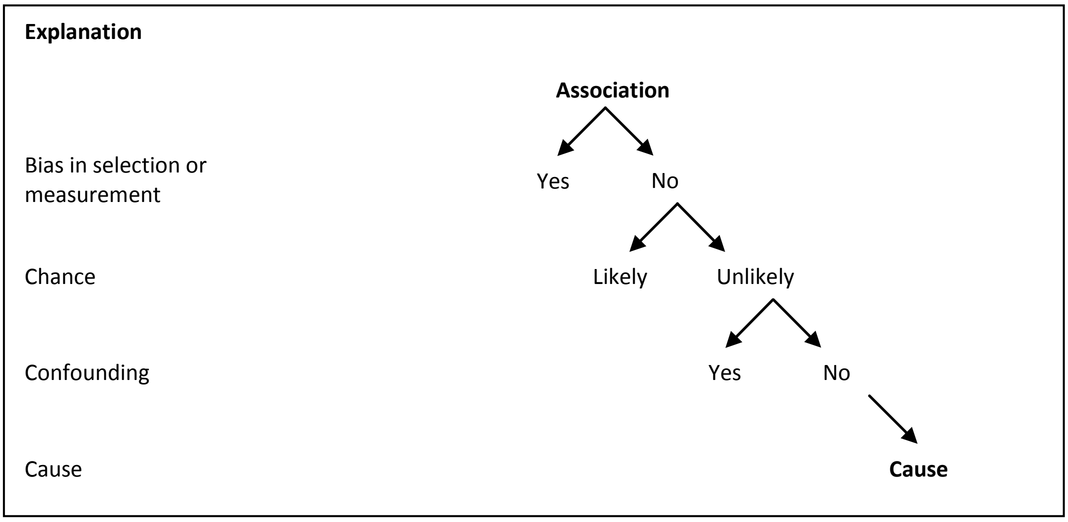
Figure 2. Comprehensive stroke service (adapted from *Stroke Units: an evidence based approach*[27]).



5.2. BIAS, CONFOUNDING AND CHANCE

When considering a potential causal relationship, it must be determined whether the observed association is an artifact from bias, confounding, or chance. As illustrated in figure 3, selection bias, information bias, confounding, and chance must be excluded before concluding that a causal association is likely.[134] Below follows a discussion of these potential pitfalls as steps to evaluate the internal validity of the four studies in this thesis.

Figure 3. Association and cause (adapted from *Clinical Epidemiology. The essentials*[134])



5.2.1. Selection bias

Selection biases are distortions that result from selection of study participants and from factors that influence study participation.[136] In case of selection bias, the relationship between exposure and outcome differs between those who participate in the study and all those who in theory were eligible for the study.[136]

All studies in this thesis identified the study population through the DNIP-stroke database independently of the exposures and outcomes in the individual studies. Participation in the Danish National Indicator Project is mandatory for all Danish hospital departments treating patients with stroke, and extensive efforts are made to ensure the completeness of patient registration in the project, including detailed written instruction for patient registration and regular comparison of the completeness of patient registration with local hospital discharge registries.[7, 22] Therefore, it seems unlikely that selection bias due to selection of study participants could have major influence on the results presented in the thesis.

A concern in most follow-up studies is loss to follow-up, which may induce selection bias if it occurs selectively according to the exposure groups or the risk of outcome.[105] In this thesis, follow-up was almost complete on mortality[108] and on the processes of care (see Table 5), which virtually precludes the risk of selection bias with respect to these outcomes. However, follow-up on the length of hospital stay (study I, III, and IV), the hospital costs (II), and one-year bed-day use was discontinued in patients who died during the study period. Because early evidence-based care and more specialized care have been linked with reduced risk of death among patients with stroke,[38, 57, 60, 77, 98] patients in high quality/specialized settings may appear to have been hospitalized longer than patients in low quality/specialized settings. The competing influence of death would in all probability distort the results towards a null-association or an association in the opposite direction than was observed in study I, II, and IV; i.e. towards an association between high quality of care/specialization and high bed-day use/cost. In study I, II, and IV, we evaluated this potential bias in sensitivity analyses where patients who died during the study period were excluded, and found virtually no indication of bias.

Missing data are common in all medical research and may produce selection bias.[130] In all four studies, we took missing data into account, and the results were in general confirmed by a complete-case analysis. This may indicate that individuals with missing data approximate a random sample of the source population, and that missing data had no major influence on the results.[105, 130]

In conclusion, the main potential sources of selection bias were due to missing data and death during follow-up, which could complicate the interpretation of the results on bed-day use and costs. These potential sources of bias were evaluated in sensitivity analyses in the individual studies and appeared to have no major influence on the results.

5.2.2. Information bias

Information bias is caused by measurement errors in the needed information. Measurement error that depends on the actual values of other variables is classified as differential misclassification and measurement error that does not depend on the actual values of the other variables is classified as nondifferential misclassification.[136]

The data used in the studies in this thesis will inevitably suffer from misclassification because the information was collected in routine clinical settings. However, the data were collected prospectively and independent of the thesis and the misclassification was, therefore, most likely nondifferential. The studies were restricted to patients who were admitted to stroke units because stroke units were expected to follow the same broad principles of acute stroke care due to mandatory participation in the Danish National Indicator Project, which promotes consistent compliance with important clinical guidelines and assessment of essential prognostic factors. Inherent variation in the registration practice between stroke units was further minimized by the use of uniform registration forms,[115] detailed written data definitions and instructions,[113] and regular structured audits at a national, regional, and local level.[7, 113] This will inevitable reduce the variation in stroke services and registration practices.

Nondifferential misclassification of a binary exposure or outcome variable results in bias towards the null.[136] Accordingly, non-differential misclassification of the registration of the individual processes of care (yes/no), the stroke unit setting (neurological/non-neurological), and mortality (dead/alive) would give bias towards the null value. This could in theory have contributed to the null-results in study III regarding the association between the stroke unit setting, some of the processes of early stroke care, and outcome. However, consistent with previous studies, study III showed that patients in neurological settings had higher odds than those in non-neurological settings of receiving diagnostic tests and secondary medical prophylaxis.[78, 81-83, 85, 86] It seems unlikely that non-differential misclassification only biased some of the associations and consequently, unlikely that information bias had any fundamental influence on the results.

In study IV, categorization of volume in quartiles may also potentially have introduced bias. The chosen cutpoints may blur an actual association if patients at high risk of outcome are subcategorized together with persons at low risk, but the cutpoints may also be chosen to maximize significance or the size of estimates.[125] Therefore, it was specified a priori that the analyses should be performed by volume quartiles in accordance with several previous studies.[91, 97, 98] The categorization was confirmed by spline curves which showed that no essential non-linear relationships were present (Figure 2).

Length of stay represented a specific problem in study III and IV (nationwide) since both acute stroke units and comprehensive stroke units (i.e. units covering both the acute phase and rehabilitation phase) were included, and consequently some inherent variation in the length of stay between the departments could be expected. However, in study IV we found a clear relationship between higher stroke unit volume and shorter length of the initial hospital stays as well as reduced hospital bed-day use when focusing on all-cause hospitalizations in the first year after stroke. The consistency in results may substantiate a true link between higher volume and shorter length of the initial hospital stay and/or lower risk of readmissions. In study I and II (the former Aarhus County), length of stay included the acute hospitalization and in-patient rehabilitation in all cases, and data on length of stay was virtually complete.

A recent Japanese study has shown that differences in costs during the acute phase of stroke may be highly influenced by ICU utilization and local management policies.[119] It has also been shown that the main cost determinants of in-hospital stroke care are the costs of nursing and physician care and overheads (i.e. fixed costs in the short term), and that the variation in costs therefore will relate closely to the length of stay.[27, 28] This indicates that our data on costs, which takes into account days spent in ICU, acute care and rehabilitation, are sound with regard to reflecting differences in hospital costs. However, cost estimates based on average charges are rough approximations and may overestimate the total costs of in-patient care.[137] Consequently, the cost estimates in study II should merely be used to reflect differences in costs between groups rather than the actual costs of inpatient care. We also calculated the potential bed-day cost savings based on a daily base charge including only nonmedical services such as food, cleaning, and electricity. This should reflect the minimal potential bed-day savings since patients with stroke usually require clinical services, e.g. rehabilitation, throughout the complete hospitalization.

In conclusion, the main potential sources of information bias lie in the risk of bias due to non-differential misclassification and complexities in interpreting the values for length of stay. However, the influence of information bias is in general believed to be low.

5.2.3. Confounding

Confounding may be considered as confusion of effects.[105, 136] To be a confounder, a variable must be associated with the exposure, be an extraneous risk factor for the outcome, and it cannot be an intermediate step in the causal path between the exposure and the outcome.[136] The main limitation of the studies in this thesis is the non-randomized design and the results may, as a consequence, be influenced by residual confounding due to the use of crude variables (e.g. using a composite crude measure of comorbidity) or unaccounted confounding (e.g. socioeconomic status[99, 138, 139]).

Furthermore, it might be of concern that the patients´ eligibility for the specific processes of care was determined by the staff because health care professionals could prioritize differently. However, evaluating the importance of early versus delayed care exclusively among patients who, based on their clinical presentation, were found eligible for care will inevitable minimize the risk of confounding-by-indication. In study III and IV, confounding caused by selective referral of patients to neurological stroke unit settings (study III) and high-volume stroke units (study IV) may have occured[44], but selective referral is less likely for medical emergencies than for elective medical care. Several precautions were taken to minimize the impact of possible confounding. We adjusted for a wide range of known prognostic factors, including age, atrial fibrillation, initial stroke severity, and hospital characteristics.[44, 87, 88, 140, 141] We also corrected for clustering of patients within stroke units, thereby taking into account unmeasured characteristics of the stroke units that may be associated with the outcomes.

The findings in study I, II, and IV were in general robust to confounder adjustment which may indicate that confounding has no crucial influence on the results. However, the unadjusted findings in study III changed in direction towards higher mortality in the neurological stroke unit settings when adjustment was made for patient and hospital characteristics, and the results must as a consequence be interpreted cautiously. Still, the finding that stroke patients with comorbid disease benefitted less than patients with no comorbid disease from care in specialized neurological settings was consistent in both unadjusted and adjusted analyses.

In conclusion, considering the non-randomized design of the studies, the results may be influenced by confounding. There is, however, no indication that confounding could change the overall conclusions of study I, II, and IV, but the results in study III should be interpreted cautiously.

5.2.4. Chance

Random error resulting from chance is inherent in all observations, and a summary measure of the statistical precision of the point estimate is needed.[142] In this thesis, the statistical precision of the point estimates were reflected by 95% confidence intervals; i.e. if the study was repeated many times, the confidence limits would contain the true value in 95% of the repetitions.[142] Several features of the studies influenced the risk of chance findings and the statistical precision of the point estimates, including the inherent variability in the data-collection, the study size, missing data, clustering of observations within the stroke units, multiple comparisons, and the number of covariates in the adjusted analyses.

The risk of chance findings was reduced by several approaches. First, imputing missing values with simple imputation techniques may have underestimated the variance and overestimated the statistical precision, but we used multiple imputation which is believed to give sound results with respect to the statistical precision because it reflects that the distribution of the variables with missing values is estimated.[130] Secondly, we used robust estimates of the variance to take into account that the observations within the stroke units may be more similar to each other than to observations in the rest of the sample and thus, took into account that the statistical precision from the regression models without cluster correction may have been overestimated.[128] However, the multiple comparisons in the individual studies had a 5% risk of the statistical significant results being chance findings.[142]

To the best of our knowledge, the studies in this thesis are among the largest population-based studies on the topics to date which lowers the risk of rejecting a true difference/association due to lack of statistical precision.

In conclusion, the main risk of chance findings was caused by multiple comparisons.

5.2.5. Summary: Internal validity

The main strengths of the studies in this thesis are the population-based designs, the detailed and prospective data collection, the almost complete follow-up on all outcomes, and the large study populations. These features minimized the risk of selection and information bias. However, the results may be affected by unaccounted confounding or residual confounding because of the observational study designs. Confounding is of most concern in study III regarding the importance of the medical specialization in stroke units, and as a consequence the results should be interpreted with caution. The findings in this thesis should be considered as associations and not as evidence of causal relationships.

5.3. EXTERNAL VALIDITY

The population-based designs of the studies, the high completeness of patient registration in the DNIP-stroke registry[22], and the global initiatives to standardize stroke care[21, 49, 50] suggest that the findings may apply to other settings. However, it is well-known that differences exist between countries in the management of patients with stroke.[143, 144] Before generalizing the findings in this thesis to other care settings, it is therefore necessary to consider whether the factors that distinguish the target populations and health care systems from the study populations and settings in this thesis could somehow modify the observed associations.

5.4. THE SCIENTIFIC EVIDENCE

5.4.1. Processes of early stroke care

We have only identified one study that addressed the association between a range of recommended processes of stroke care and economic outcome.[66] The study is an Italian cohort study, which demonstrated that a high compliance rate with 47 clinical guidelines recommended by the American Heart Association was associated with reduced hospital costs and according to descriptive analyses, the cost savings were ascribed to shorter length of stay.[60, 66] Potential cost savings have also been demonstrated with regard to accelerated, immediate pre-hospital diagnostic evaluation and treatment in an outpatient clinic, early mobilization, and treatment with thrombolysis.[70, 72, 73] Hence, the results of previous studies were in accordance with the findings in study I and II.

The prominent association between early mobilization and reduced length of stay (study I) as well as reduced hospital costs (study II) was supported by an Australian study. The study showed that early mobilization in addition to standard care incurs significantly less costs at 3 and 12 months compared with standard care alone, largely attributable to less bed-days in inpatient rehabilitation.[73] Study I and II also suggested that early admission to a stroke unit may be associated with potential hospital cost savings and thus, the results supports the international guidelines recommending that patients with stroke should be admitted to stroke units in the acute phase of stroke.[21, 50, 112, 145]

Receiving more processes of evidence-based care in the early phase of stroke has been linked with reduced risk of mortality and medical complications[38, 39] as well as reduced length of hospital stay and hospital costs. It can therefore be hypothesized that early intensive evidence-based stroke care is a cost-effective approach to treating patients with stroke. Still, several issues need to be clarified before a conclusion can be made. Issues for future research include the actual costs of providing early versus delayed care, the specific short- and long-term economic consequences from a societal perspective (e.g. the rehabilitation costs for the municipalities and costs of institutional care), and other health consequences (e.g. disability and quality of life).

5.4.2. Medical setting

According to a number of studies, stroke patients have better survival when cared for by neurologists compared with other specialists, [78, 81, 85, 92, 101] but some studies showed null results.[80, 83, 86] Only one study has specifically addressed the relationship between the medical specialty in stroke units and patient outcome.[77] The study is an Italian follow-up study of 11572 acute stroke patients, which found no difference in the risk of death or disability whether or not stroke units only had neurological beds (OR 0.88; 95% CI: 0.55-1.39). The study did, however, find a reduced risk of death and disability in conventional wards with only neurological beds (the wards had neither beds nor staff dedicated to stroke patients) (OR 0.64; 95% CI: 0.55-0.75). The study was not population-based and made incomplete or no adjustment for potential important confounding factors, such as stroke severity and comorbid disease. Even so, our study supports their findings; i.e. that the stroke unit setting has no overall association with patient outcome. Stroke units are characterized by intensive stroke specialization through continuous education of the staff and a well-established clinical practice, including the use of CT or MRI scan and multidisciplinary rehabilitation,[55,54] and these characteristics may be among the components that diminish the potential basic differences between the primary medical specialties in stroke units. Alternatively, the null-result in relation to mortality may reflect that mortality as outcome was insensitive to detect underlying changes in patient prognosis.

To the best of our knowledge, study III is the first to specifically address the association between stroke unit setting and timely evidence-based care. However, the findings in study III are in accordance with a number of follow-up studies, not restricted to stroke units.

These studies found that stroke patients seen by neurologists are more likely than those not seen by neurologists to receive diagnostic tests, including MRI scan, and secondary medical prophylaxis, including ticlopidine, warfarin, heparin, and heparinoid.[78, 81-83, 85, 86]

Only few other studies have focused on the relationship between health care specialization and comorbid disease among patients with cardiovascular diseases, and these studies suggest that patients with comorbid disease benefit less from specialized treatment than healthier patients.[78, 120, 82] A study on stroke patients showed that patients with atrial fibrillation had worse survival when cared for in neurology services compared with general services, whereas patients without atrial fibrillation had better survival when cared for on neurology services.[82] Another study on stroke patients showed that patients in neurology services had increased risk of rehospitalization with heart disease compared with patients cared for in general services.[78] Furthermore, a study on patients undergoing coronary artery bypass graft surgery demonstrated that patients with comorbid disease experienced higher 30-day postdischarge mortality when treated at cardiac specialty hospitals than patients treated at less specialized hospitals,[120] but in contrast there was no association between specialization and mortality among healthier patients. Although we were unable to demonstrate any statistically significant differences between stroke patients with no, moderate and severe comorbid disease, our results did indicate that stroke patients with moderate comorbid disease benefit less from neurological specialized care than stroke patients without comorbid disease. These results may be chance findings, but it cannot be ruled out that stroke patients with moderate comorbid disease are not treated optimally in specialized neurological settings. Further studies are warranted to further clarify this issue.

In conclusion, the findings in study III are in general supported by the scientific literature. However, only one identified study focused specifically on stroke units.

5.4.3. Volume

In study IV, we did not find a link between higher volume and lower mortality like most previous studies.[88, 90, 97-102] The null-result in relation to mortality may reflect that the intensive stroke specialization in stroke units levels off the scale effect with respect to better clinical outcome. This is consistent with a single study, specifically restricted to stroke units, which found no difference in the risk of death or disability between patients admitted to stroke units treating more than 100 patients per year and patients admitted to stroke units treating less than 100 patients per year.[77] Figure 2 cautiously suggests that the scale advantages in stroke units are most evident in small-scale stroke units. This is compatible with several economic studies suggesting that the scale effect diminishes or even becomes reverse in large-scale institutions.[27, 93-95] Alternatively, focusing merely on mortality as outcome may be insensitive to detect underlying changes in patient prognosis, and studies focusing on other clinical outcomes are warranted (e.g. disability and medical complications).

A Taiwanese study showed that higher physician volume was associated with reduced hospital costs among stroke patients, after adjusting for patient, physician, and hospital characteristics.[90] The study described length of stay as a key mediator in this association, and further suggested that the favorable volume-cost relationship could be ascribed to more cost-effective and technically effective medical treatment skills and more efficient coordination of the various treatment elements and discharge planning in relation to higher case volume.[90, 94]

Missing from most research is an exploration of the mechanisms through which volume influences outcome.[44] Only three studies were identified that compared processes of stroke care between high and low volume hospitals. One study showed that a higher number of hospital beds was associated with increased guideline compliance;[91] the other studies found no direct link between volume and guideline compliance.[3, 96] Still, adjustment for the received processes of care had no major influence on the results in study IV, suggesting that other factors also contribute to the reduced length of stay and one-year bed-day use in high-volume stroke units.

Similar to study III, the findings in study IV are in general in accordance with other scientific publications. However, only one identified study focused specifically on stroke units.

6. CONCLUSIONS

STUDY I AND II

Receiving specific evidence-based processes of care in the early phase of stroke was associated with shorter length of hospital stay and potential hospital cost savings among patients with stroke. Receiving more evidence-based processes of early stroke care appeared to follow a dose-response relationship with shorter length of hospital stay and a potential of further savings.

STUDY III

Patients with stroke received earlier CT or MRI scan and earlier antiplatelet therapy when admitted to neurological stroke unit settings compared with non-neurological settings. No indications of differences were found between patients admitted to neurological and non-neurological settings with regard to other essential processes of early stroke care, mortality, readmissions, and length of hospital stay.

The study indicated that stroke patients with comorbid disease may benefit less than stroke patients without comorbid disease from neurological specialized care; however this finding remains to be confirmed by other studies.

STUDY IV

Patients with stroke who were admitted to high-volume stroke units received more evidence-based processes of care in the early phase of stroke and spent fewer days in hospital during the first year after stroke compared with patients who were admitted to low-volume stroke units. There was no indication that stroke unit volume was associated with short- or long-term mortality.

7. PERSPECTIVES

The Danish health care system provides unique possibilities for identifying overall links between health care performance, clinical outcome, and resource utilization in stroke care due to the availability of detailed and updated nationwide information. This thesis has identified some general characteristics of modern stroke care which may guide clinicians and health care decision-makers, and provide a basis for future research.

First, the thesis underlines the need for continued efforts to ensure a high quality of care in the early phase of stroke through adherence to clinical guidelines. In particular early mobilization appears important in relation to both patient prognosis and the costs of stroke care,[38, 39, 56, 73] and mobilization within the first few days seems to be well tolerated and not harmful.[146] The thesis also acknowledges the importance of data registration in the Danish National Indicator Project. The registry provides invaluable clinical information, but the total number of patients with missing data is large although patients have relatively few missing data on the individual variables. Further improvement in registration would optimize the foundation for clinical improvements and research applicability. Study I, II, and IV identified a potential for reduced bed-day use in relation to early evidence-based care and high case volume in stroke units. However, to obtain a real value of the bed-day savings, the saved bed-days should be realized in monetary values or the freed capacity should be transferred to other health care areas.

This thesis also identifies potential areas for future research. First, it would be valuable to identify the underlying mechanisms for reduced bed-day use in relation to early evidence-based care and high case volume in order to better understand their clinical and administrative implications. Study II indicated that some, but far from all of the association between receiving more processes of care and lower hospital costs was mediated through the prevention of medical complications, but other studies suggest that prevention of medical complications through early evidence-based care may play an important role in reducing the length of hospital stay.[39, 56, 147] The underlying mechanisms for economies of scale in high-volume institutions are also complex and unclear. Study III suggested that patients admitted to high-volume stroke units received more processes of care in the early phase of stroke which may support the general assumption that more efficient working procedures in high-volume institutions may contribute to reduced average costs per patient.[90, 94] Future research should focus on the complete care pathway, including the importance of discharge planning in reducing the length of hospital stay.[90] It must also be clarified whether reduced bed-day use is associated with an extra burden on community services.

It may be hypothesized that early intensive evidence-based stroke care and care in high-volume stroke units are cost-effective approaches to treating patients with stroke because the evidence suggests that early evidence-based stroke care and high case volume is associated with better clinical outcome[38, 39, 88, 90] as well as potential cost savings[66, 90]. Several issues will need to be clarified before more conclusive answers can be reached, including the specific costs of providing early evidence-based care, the specific costs of care in high-volume versus low-volume departments, the short- and long-term economic consequences from a societal view (such as the rehabilitation costs after discharge and the costs of institutional care), and other short- and long-term health consequences (such as disability, quality of life, and patient satisfaction).

Finally, it is also important to assess the impact of further specialization in the modern health care system which is characterized by being increasingly specialized, and to assess whether patients with comorbid disease benefit from specialized care. Coordination of care for patients with multiple chronic conditions may be a significant challenge in specialty-oriented health care systems.[43]

8. SUMMARY

Stroke is a major public health challenge given its high incidence, high mortality, high morbidity among the survivors, and high economic costs. Early evidence-based care may have a beneficial effect on stroke outcome, but little is known about the economic consequences of early evidence-based care with regard to a range of recommended processes of early stroke care. Furthermore, patients may benefit from specialized care with regard to the medical specialization and scale effects, but it is uncertain whether the anticipated differences can be found in modern stroke care. The main purpose of this thesis was to identify links in health care quality by examining overall associations between selected aspects of specialization (medical specialization and case volume), processes of early stroke care, mortality, and hospital bed-day use among patients with stroke.

The thesis is based on four population-based cohort studies using data from Danish population-based medical registries (the Danish National Indicator Project, the National Registry of Patients, the Civil Registration System, and the classification of Danish Hospitals and Departments) as well as local hospital charges. The study population included patients with acute stroke who were admitted to a stroke unit during 2003-2010. Data on exposure, outcome, and covariates were collected prospectively and independent of the thesis. The processes of care reflected whether consensus recommendations for the early management of patients with stroke were followed. Follow-up was almost complete on all outcomes.

Study I-IV included between 2,639 and 63,995 patients with stroke admitted to Danish stroke units. Study I and II showed that receiving evidence-based processes of care in the early phase of stroke was associated with reduced length of hospital stay and potential hospital cost savings among patients with stroke. Patients who received between 75% and 100% of the processes of care in the early phase of stroke were hospitalized about half as long and incurred approximately half the costs as patients who received between 0% and 25% (adjusted ratio of length of stay: 0.53, 95% CI: 0.48-0.59, and adjusted ratio of hospital costs: 0.52, 95% CI: 0.39-0.70). Study III showed that, except for early antiplatelet therapy and early CT/MRI scan, the medical specialty in stroke units was not associated with other

differences in essential processes of early stroke care, mortality, readmissions, and length of hospital stay. Study IV showed that patients who were admitted to high-volume stroke units received more processes of care in the early phase of stroke compared with patients in low-volume stroke units (unadjusted difference: 9.84 percentage points, 95% CI: 3.98-15.70). Higher volume was also associated with shorter length of the initial hospital stay (adjusted ratio: 0.49, 95% CI: 0.41-0.59) and reduced bed-day use in the first year after stroke (adjusted ratio: 0.79, 95% CI: 0.70-0.87), whereas no association was found with mortality.

In conclusion, early intensive evidence-based stroke care may be associated with reduced length of hospital stay and potential cost savings to the hospitals. Furthermore, patients admitted to high-volume stroke units may receive a higher quality of early stroke care and have fewer in-hospital bed-days during the first year after stroke compared with patients admitted to low-volume stroke units, but no association with mortality was observed. Except for early CT or MRI scan and early antiplatelet therapy in neurological stroke unit settings, the medical setting of stroke units appeared unrelated with other essential processes of early stroke care, mortality, readmissions, and length of hospital stay.

9. DANISH SUMMARY

Apopleksi udgør en væsentlig samfundsmæssig udfordring, idet sygdommen er karakteriseret ved en høj incidens, høj dødelighed, høj forekomst af nedsat funktionsevne blandt de overlevende, og store omkostninger for samfundet. Tidlig evidensbaseret behandling er sandsynligvis forbundet med bedre klinisk outcome hos patienter med apopleksi, men der er begrænset evidens for de økonomiske konsekvenser af tidlig evidensbaseret behandling i henhold til en række konsensus anbefalinger for den akutte behandling af patienter med apopleksi. Herudover er mere specialiseret behandling med hensyn til medicinsk specialisering og stordrift sandsynligvis forbundet med bedre klinisk outcome, men det er uklart, om de formodede sammenhænge kan genfindes i den moderne apopleksibehandling. Hovedformålet med denne ph.d.-afhandling var at identificere sammenhænge i sundhedsvæsenets kvalitet indenfor apopleksi ved at undersøge overordnede associationer mellem forskellige aspekter af specialisering (medicinsk speciale og volumen), processer i den tidlige apopleksibehandling, mortalitet, og sengedagsforbrug blandt patienter med apopleksi.

Afhandlingen blev baseret på fire kohorte undersøgelser, som anvendte data fra danske befolkningsbaserede medicinske registre (det Nationale Indikator Projekt, Landspatientregistret, det Centrale Personregister og Sygehus- og afdelingsklassifikationen) og lokale sygehusdata vedrørende omkostninger. Studiepopulationen inkluderede alle patienter med akut apopleksi, som blev indlagt på et apopleksiafsnit i perioden 2003-2010. Data om eksponering, outcome, og kovariable blev indsamlet prospektivt og uafhængigt af afhandlingen. Behandlingsprocesserne afspejlede, hvorvidt konsensusanbefalinger for den tidlige behandling af patienter med apopleksi blev fulgt. Follow-up var næsten komplet for alle outcomes.

Studie I-IV inkluderede mellem 2,639 og 63,995 patienter med apopleksi som var indlagt på apopleksiafsnit i Danmark. Studie I og II viste, at tidlig evidensbaseret behandling var forbundet med korterevarende indlæggelse og reducerede sygehusomkostninger blandt patienter med apopleksi. Indlæggelsesvarigheden og omkostningerne var næsten halveret hos patienter som modtog mellem 75% og 100% af de anbefalede behandlingsprocesser i den tidlige fase af apopleksien sammenlignet med de patienter, som modtog mellem 0% og 24% (justeret ratio af indlæggelseslængde: 0,53, 95% CI: 0,48-0,59 og justeret ratio af omkostninger: 0,52, 95% CI: 0,39-0,70). Studie III viste, at bortset fra tidlig CT eller MR-scanning og tidlig trombocythæmmende behandling på apopleksiafsnit med neurologisk speciale, var det medicinske speciale på apopleksiafsnit ikke forbundet med forskelle i andre essentielle behandlingsprocesser, mortalitet, genindlæggelse eller indlæggelsesvarighed. Studie IV viste, at patienter, som blev indlagt på apopleksiafsnit med højt patient-volumen, modtog flere behandlingsprocesser i den tidligere fase af apopleksien sammenlignet med patienter, som blev indlagt på apopleksiafsnit med lavt patient-volumen (ukorrigerede absolut forskel: 9,84 procentpoint, 95% CI: 3,98-15,70). Højere volumen var også forbundet med kortere indlæggelsesvarighed i forbindelse med den initiale indlæggelse for apopleksi (justeret ratio: 0,49, 95% CI: 0,41-0,59) og færre sengedage på hospitalet i det første år efter apopleksien (justeret ratio: 0,79, 95 % CI: 0,70-0,87). Der blev ikke observeret nogen sammenhæng mellem apopleksiafsnittenes volumen og patienternes mortalitet.

Sammenfattende viser afhandlingen, at tidlig evidensbaseret behandling sandsynligvis er forbundet med korterevarende indlæggelser for patienter med apopleksi og potentielle besparelser for sygehusene. Desuden er højere patientvolumen på apopleksiafsnit sandsynligvis forbundet med højere kvalitet i den tidlige apopleksibehandling og færre sengedage på hospitalet i det første år efter en apopleksi, men der blev ikke observeret nogen sammenhæng mellem volumen og patienternes mortalitet. Udover tidlig CT eller MR-scanning og tidlig trombocythæmmende behandling på apopleksiafsnit med neurologisk speciale, var det medicinske speciale på apopleksiafsnit ikke forbundet med forskelle i andre essentielle behandlingsprocesser, mortalitet, genindlæggelse eller indlæggelsesvarighed.

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11. PhD ARTICLES

Quality of Care and Length of Hospital Stay Among Patients With Stroke

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Background: The relationship between quality of care and economic outcome measures, including length of stay (LOS), among patients with stroke remains to be clarified.

Objectives: To determine whether quality of care is associated with LOS among patients with stroke.

Methods: In this population-based follow-up study, we included 2636 patients with stroke who had been admitted to dedicated stroke units in Aarhus County, Denmark, from 2003 to 2005. Quality of care was measured as fulfillment of 12 criteria: early admission to a stroke unit, early antiplatelet therapy, early anticoagulant therapy, early computed tomography/magnetic resonance imaging scan, early water swallowing test, early mobilization, early intermittent catheterization, early deep venous thromboembolism prophylaxis, early assessment by a physiotherapist and an occupational therapist, and early assessment of nutritional and constipation risk. Data were analyzed by linear regression clustered at the stroke units by multilevel modeling.

Results: Median LOS was 13 days (25th and 75th percentiles: 7, 33). Meeting each quality of care criteria was associated with shorter LOS. Adjusted relative LOS ranged from 0.67 (95% confidence interval (CI): 0.61–0.73) to 0.87 (95% CI: 0.81–0.93). The association between meeting more quality of care criteria and LOS followed a dose-response effect, that is, patients who fulfilled between 75% and 100% of the quality of care criteria were hospitalized about one-half as long as patients who fulfilled between 0% and 24% of the criteria (adjusted relative LOS: 0.53, 95% CI: 0.48–0.59).

Conclusions: Higher quality of care during the early phase of stroke was associated with shorter LOS among patients with stroke.

Key Words: stroke, quality of care, length of stay

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Stroke has a substantial economic impact, consuming 2% to 4% of the total health care costs in developed countries.[1,2] The cost of inpatient treatment is one of the most significant cost component during the first year after stroke[1,2] and the hospital costs are highly correlated with the patients' length of stay (LOS).[3]

A number of observational studies have linked higher quality of care, determined by compliance with specific processes of care, with reduced risk of death and disability among patients with stroke.[4–8] A positive association has been reported for overall guideline compliance in most studies,[4,5,8] and some studies have also reported positive associations for separate processes of care, ie, initiation of antiplatelet therapy, swallowing assessment, and assessment by a physiotherapist.[6,7]

Although hospital stroke care is very cost-intensive,[1,2] so far only 2 studies have examined the association between quality of care in terms of compliance with specific processes of care and economic outcome measures.[9,10] Quaglini et al found that guideline compliance was associated with hospital cost savings and, based on descriptive analyses, the cost savings were ascribed to shorter LOS.[9] Further, an Australian study showed that early mobilization in addition to standard care incurs significant less cost compared with standard care alone.[10] We, therefore, examined whether fulfillment of specific evidence-based quality of care criteria for early intensive care affected LOS among patients with stroke who had been admitted to dedicated stroke units.

METHODS

In this population-based follow-up study we included all patients with stroke who had been admitted to dedicated stroke units in Aarhus County, Denmark, and discharged between January 13, 2003 and November 1, 2005 (n = 2636).

The Danish National Health Service provides tax-supported health care for all inhabitants of Denmark, including free access to hospital care.[11] Since 1968, all Danish residents have been assigned a unique civil registration number that is used in all health databases and permits unambiguous record linkage.[11] The primary data source for this study was the Danish National Indicator Project (DNIP),[12] supplemented by information on Charlson Comorbidity Index from the Danish National Registry of Patients.[13]

The Danish National Indicator Project

In 2000, DNIP was established as a nationwide quality improvement project.[12] The project targets documentation, monitoring, and improving the quality of treatment and care for patients with 8 specific diseases, including stroke.[12] Data on quality of care, in accordance with fulfillment of specific quality of care criteria, and on patient characteristics are collected prospectively upon hospital admission by the staff caring for the patients, using a standardized registration form with separate data specifications. Participation in DNIP is mandatory for all hospitals and relevant clinical departments in Denmark that treat patients with the 8 diseases in question.[12]

The Danish National Registry of Patients

The Danish National Registry of Patients was established in 1977 and includes data on all hospitalizations from nonpsychiatric hospitals in Denmark. Among other variables, it includes data on dates of admission and discharge, and up to 20 discharge diagnoses assigned by the treating physician.[13]

Study Population

Patients 18 years of age or older are eligible for inclusion in the DNIP database if they are hospitalized with stroke according to the WHO criteria, ie, rapidly developing symptoms and signs of focal or global neurologic dysfunction of presumed vascular etiology lasting more than 24 hours or leading to death.[14] Thus, patients with intracerebral hemorrhage, cerebral infarction, or unspecified stroke are included in the DNIP database. Patients with subdural hematoma, subarachnoidal or epidural hemorrhage, retinal infarct, and infarct caused by trauma, infection, surgery, or an intracerebral malignant process are not included. Patients with diffuse symptoms, such as isolated vertigo, and asymptomatic patients with infarct detected only by computed tomography (CT) or magnetic resonance imaging (MRI) scan are also excluded.

Through the DNIP database, we identified all patients with stroke who were discharged from a hospital in Aarhus County between January 13, 2003 and November 1, 2005 (n = 3385). Aarhus County is a well-defined geographic area with approximately 650,000 inhabitants. Although 169 patients had multiple events during the study period, this study included only the first stroke event registered in the DNIP during that period. Patients who were not admitted to a stroke unit (n = 749) were excluded leaving a total of 2636 patients available for analyses, of whom 184 patients died during hospitalization. This study included data from 7 stroke units.

Quality of Care Criteria

The quality of care criteria demonstrate whether diagnosis, treatment, and care conform to nationally and internationally recommended clinical guidelines for acute care of patients with stroke.[15–18]

In DNIP, a national expert panel including physicians, nurses, physiotherapists, and occupational therapists identified the quality of care criteria covering the acute phase of stroke based on a systematic review of the scientific literature.[12] The literature review was done by a clinical epidemiologist in accordance with the methodology used by the Scottish Intercollegiate Guidelines Network (SIGN).[19] When selecting 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. A time frame was defined for each criterion to capture the timeliness of the interventions. The timing of the interventions was recorded as a date rather than time of the day (Table 1). The criteria included early admission to a stroke unit, early initiation of antiplatelet or anticoagulant therapy, early CT/MRI scan, early assessment by a physiotherapist, early assessment by an occupational therapist, and early assessment of nutritional risk. A specialized stroke unit was defined as a hospital department/unit that exclusively or primarily is dedicated to patients with stroke and characterized by multidisciplinary teams, staff with specific interest in stroke, the involvement of relatives, and continuous education of the staff. Initiation of antiplatelet and anticoagulant therapy was defined as continuous use of the drugs and not merely a single dose. Assessment by a physiotherapist and an occupational therapist was defined as formal bedside assessment of the patient's need for rehabilitation, and assessment of nutritional risk was defined as assessment following the recommendations of the European Society for Parenteral and Enteral Nutrition (ie, calculation of a score that accounts for both the nutritional status and the stress induced by the stroke).[20] In Aarhus County, the DNIP database includes an extended registration of quality of care criteria, and in addition to the aforementioned criteria this study included criteria on early swallowing assessment, early assessment of constipation risk, early mobilization, early intermittent catheterization, and early venous thromboembolism prophylaxis. Swallowing assessment was defined as formal bedside water swallowing test before the patient was given food and drink. Constipation risk assessment was defined as assessment of the patient's risk of constipation upon admission. Mobilization was defined as assisting the patient from bed-rest, intermittent catheterization was defined as the use of a sterile intermittent catheterization technique, and venous thromboembolism prophylaxis was defined as treatment with low-molecular-weight heparin or compression stockings.

Patients were excluded from analysis of each of the 12 quality of care criteria if the process of care was deemed contraindicated by the stroke team or treating physician or if data were missing on the criterion in the DNIP database. Thus, the number of patients included in analyses of the specific criteria varied (Table 2). Patients were classified as eligible or ineligible for fulfillment of the specific quality of care criteria depending on whether the stroke team or treating physician identified contraindications, such as gastrointestinal bleeding precluding early antiplatelet therapy and rapid spontaneous recovery of motor symptoms making early mobilization irrelevant. Patients who received a "do not resuscitate" order were in general not considered to be candidates for the quality of care measures. The quality of care criteria were categorized as Yes (the quality of care criteria fulfilled within the time frame) and No (the quality of care criteria fulfilled during hospitalization, but not within the time frame,

TABLE 1. Descriptive Characteristics (n=2636)

Characteristics	
LOS, median (25, 75 quartiles)	
Stroke unit 1	11 (7, 17)
Stroke unit 2	16 (8, 27)
Stroke unit 3	14 (8, 32)
Stroke unit 4	10 (5, 29)
Stroke unit 5	21 (11, 39)
Stroke unit 6	20 (8, 40)
Stroke unit 7	9 (4, 30)
Combined	13 (7, 33)
Age, n (%)	
≤65	772 (29.3)
>65–≤80	1188 (45.1)
>80	676 (25.6)
Gender, n (%)	
Male	1432 (54.3)
Marital status, n (%)	
Living with someone	1423 (54.5)
Living alone	1145 (43.9)
Other form of marital status	43 (1.6)
Housing, n (%)	
Own home	2377 (91.7)
Nursing home/institution	173 (6.7)
Other form of housing	42 (1.6)
Profession, n (%)	
Pensioner	2059 (80.2)
Employed/unemployed	456 (17.8)
Other form of profession	51 (2.0)
Alcohol intake, n (%)	
More than 14/21 drinks/wk for women/men	186 (8.3)
Smoking habits, n (%)	
Never	776 (33.0)
Daily	978 (41.7)
Occasionally	40 (1.7)
Former (quit more than $\frac{1}{2}$ yr previous)	554 (23.6)
Modified Rankin Scale Score before admission, n (%)	
No symptoms at all, 0	1355 (58.7)
No significant disability despite symptoms, 1	357 (15.5)
Slight disability, 2	261 (11.3)
Moderate disability, 3	180 (7.8)
Moderately severe disability, 4	140 (6.1)
Severe disability, 5	15 (0.6)
Atrial fibrillation, n (%)	479 (18.8)
Hypertension, n (%)	1338 (53.5)
Hyperlipidaemia, n (%)	945 (41.6)
Charlson Comorbidity Index, n (%)	
No, 0	1356 (51.4)
Moderate, 1–2	863 (32.7)
Severe, ≥3	417 (15.8)
Scandinavian Stroke Scale Score on admission, n (%)	
Mild, 45–58	1212 (55.9)
Moderate, 30–44	466 (21.5)
Severe, 15–29	281 (12.9)
Very severe, 0–14	211 (9.7)
Type of stroke, n (%)	
Ischemic	1769 (67.1)
Intracerebral hemorrhage	295 (11.2)
Unspecified	572 (21.7)
Transfer to a rehabilitation unit, n (%)	382 (14.5)
Year of hospitalization, n (%)	
2003	870 (33.0)
2004	1026 (38.9)
2005	740 (28.1)
Stroke unit (by the second day), n (%)*	
Yes	2055 (78.0)
No	581 (22.0)
Antiplatelet therapy (by the second day), n (%)	
Yes	1242 (59.8)
No	480 (23.1)
Not relevant/contraindicated	355 (17.1)
Anticoagulant therapy (by the 14th day), n (%)	
Yes	177 (8.3)
No	81 (3.8)
Not relevant/contraindicated	1886 (88.0)
CT/MRI scan (by the second day), n (%)	
Yes	2306 (87.7)
No	314 (11.9)
Not relevant/contraindicated	8 (0.3)
Physiotherapy assessment (by the second day), n (%)	
Yes	1093 (42.4)
No	1231 (47.7)
Not relevant/contraindicated	255 (9.9)
Occupational therapy assessment (by the second day), n (%)	
Yes	1032 (40.0)
No	1322 (51.3)
Not relevant/contraindicated	223 (8.7)
Nutritional risk assessment (by the second day), n (%)	
Yes	969 (39.9)
No	1126 (46.4)
Not relevant/contraindicated	331 (13.6)
Swallowing assessment (by the second day), n (%)	
Yes	1168 (47.8)
No	289 (11.8)
Not relevant/contraindicated	985 (40.3)
Assessment of constipation risk (by the second day), n (%)	
Yes	362 (15.2)
No	648 (27.2)
Not relevant/contraindicated	1371 (57.6)
Mobilization (by the second day), n (%)	
Yes	1662 (65.8)
No	487 (19.3)
Not relevant/contraindicated	375 (14.9)

(*Continued*)

TABLE 1. (*Continued*)

Characteristics	
Intermittent catheterization (by the second day), n (%)	
Yes	224 (9.7)
No	147 (6.4)
Not relevant/contraindicated	1939 (83.9)
Venous thromboembolism prophylaxis (by the second day), n (%)	
Yes	198 (9.1)
No	276 (12.6)
Not relevant/contraindicated	1709 (78.3)

*The study population includes only patients who were admitted to a stroke unit.

or the quality of care criteria not fulfilled during hospitalization) (Table 2). The proportions of quality of care criteria fulfilled were categorized as 0%–24%, 25%–49%, 50%–74%, and 75%–100% of all relevant quality of care criteria (Table 3).

This study did not include any criteria on thrombolysis because only 9 patients (0.4%) received thrombolysis during the study period.

Length of Hospital Stay

LOS included both the acute inpatient hospital stay and the inpatient rehabilitation stay. Restricting the analyses to the acute inpatient hospital stay yielded similar results and thus, we only present the results for total LOS.

LOS was defined as the time span from hospital admission to hospital discharge. The admission date was defined as the date the patient was admitted to the hospital with stroke or the date of stroke occurrence if the patient was already hospitalized with disease apart from stroke. The discharge date was defined as the date of discharge to home, a nursing home, or death. If patients were transferred between hospital departments, including transfer to a distinct rehabilitation ward, the days spent in all hospital departments were included in LOS. After acute care in stroke units, 382 patients (14.5%) received rehabilitation in a distinct rehabilitation ward.

Covariates

This study included covariates on age (≤65, >65 to 80, and >80 years), gender, marital status (living with a partner/family/friend, living alone, other form of marital status), housing (own home, nursing home/institution, other form of housing), profession (pensioner, employed/unemployed, other form of profession), alcohol intake (up to 14/21 vs. greater than 14/21 drinks per week for women/men), smoking habits (daily, occasionally, former, never), Modified Rankin Scale Score before admission (0, no symptoms at all; 1, no significant disability; 2, slight disability; 3, moderate disability; 4, moderately severe disability; 5, severe disability), atrial fibrillation, hypertension, hyperlipidemia, Charlson Comorbidity Index (0, no comorbidity; 1–2, low comorbidity; ≥3, high comorbidity), Scandinavian Stroke Scale Score (SSS) on admission (0–14, very severe; 15–29, severe; 30–44, moderate; 45–58, mild), type of stroke (International Classification of Diseases, 10th revision: I63, infarction; I61, hemorrhage; I64, unspecified), year of hospital admission (2003, 2004, 2005), and transfer to a rehabilitation unit after index hospitalization in a stroke unit.

Modified Rankin Scale Score reflects the patient's functional disability.[21,22] The interrater reliability of the modified Rankin Scale is good across multiple raters with different professional backgrounds, although disagreement by one category is common.[23] Charlson Comorbidity Index is a useful measure of comorbidity for stroke outcome studies[24] and yields strong prognostic information with respect to in-hospital mortality.[25] SSS is used to assess admission stroke severity.[26] This scale is a validated and widely-used neurologic stroke scale for evaluating the level of consciousness, eye movement, power in arm, hand, and leg, orientation, dysphasia, facial paresis, and gait.[26] SSS can be assessed

TABLE 2. Fulfillment of the Specific Quality of Care Criteria and Length of Stay (LOS)

Quality of Care Criteria (Time Frame)	n, Yes/No	Crude Ratio of LOS (95% CI)*	Adjusted Ratio of LOS (95% CI)*†
Stroke unit (by the second day)	2055/581	0.65 (0.59–0.73)	0.71 (0.65–0.77)
Antiplatelet therapy (by the second day)	1242/480	0.77 (0.68–0.86)	0.80 (0.73–0.87)
Anticoagulant therapy (by the 14th day)	177/81	0.74 (0.57–0.98)	0.78 (0.62–0.98)
CT/MRI scan (by the second day)	2306/314	0.91 (0.80–1.04)	0.82 (0.74–0.91)
Physiotherapy assessment (by the second day)	1093/1231	0.79 (0.72–0.87)	0.87 (0.81–0.93)
Occupational therapy assessment (by the second day)	1032/1322	0.76 (0.70–0.83)	0.85 (0.80–0.91)
Nutritional risk assessment (by the second day)	969/1126	0.73 (0.66–0.81)	0.83 (0.77–0.90)
Swallowing assessment (by the second day)	1168/289	0.65 (0.56–0.76)	0.78 (0.69–0.87)
Assessment of constipation risk (by the second day)	362/648	0.52 (0.46–0.59)	0.70 (0.63–0.78)
Mobilization (by the second day)	1662/487	0.42 (0.38–0.47)	0.67 (0.61–0.73)
Intermittent catheterization (by the second day)	224/147	0.72 (0.58–0.90)	0.77 (0.64–0.92)
Venous thromboembolism prophylaxis (by the second day)	198/276	0.80 (0.66–0.96)	0.82 (0.71–0.95)

*All the analyses are clustered at the stroke unit level by random effect modeling.
†Adjusted for age, gender, marital status, housing, profession, alcohol intake, smoking habits, Modified Rankin Scale Score before admission, atrial fibrillation (except for criteria on antiplatelet and anticoagulant therapy), hypertension, hyperlipidemia, Charlson Comorbidity Index, Scandinavian Stroke Scale Score on admission, type of stroke (except for criteria on antiplatelet and anticoagulant therapy), transfer to a rehabilitation ward, and year of hospitalization.

TABLE 3. The Proportion of Quality of Care Criteria Fulfilled and Length of Stay (LOS)

Proportion of Criteria Fulfilled	n (%)	Median LOS (25th and 75th Quartiles)	Crude Ratio of LOS (95% CI)*	Adjusted Ratio of LOS (95% CI)*†
0%–24%	332 (12.6)	26 (13, 58)	1	1
25%–49%	593 (22.5)	17 (9, 37)	0.67 (0.58–0.78)	0.77 (0.69–0.86)
50%–74%	816 (31.0)	13 (7, 33)	0.56 (0.49–0.64)	0.67 (0.60–0.75)
75%–100%	893 (33.9)	9 (5, 20)	0.39 (0.34–0.45)	0.53 (0.48–0.59)

*All the analyses are clustered at the stroke unit level by random effect modeling.
†Adjusted for age, gender, marital status, housing, profession, alcohol intake, smoking habits, Modified Rankin Scale Score before admission, atrial fibrillation, hypertension, hyperlipidemia, Charlson Comorbidity Index, Scandinavian Stroke Scale Score on admission, type of stroke, transfer to a rehabilitation ward, and year of hospitalization.

reliably either face-to-face[27] or from routine hospital admission records.[28]

In a sensitivity analysis, medical complications during hospitalization, including pneumonia, urinary tract infection, stroke related falls, deep venous thrombosis, and pulmonary embolism, were also included as covariates. This study was approved by The Danish Data Protection Agency (J# 2008-41-2562).

Statistical Analysis

The associations between the 12 quality of care criteria and LOS were examined separately by simple linear regression analysis and multivariable linear regression analysis, adjusting for all 16 covariates. Atrial fibrillation and stroke type were not included as covariates in analyses of the criteria on antiplatelet therapy and anticoagulant therapy because only patients with ischemic stroke and without atrial fibrillation fulfilled the criteria for antiplatelet therapy and only patients with ischemic stroke and atrial fibrillation fulfilled the criteria for anticoagulant therapy. The association between the proportion of fulfilled quality of care criteria and LOS was also examined by simple and multivariable linear regression analyses, adjusting for all 16 covariates. To account for service variability, clustering at the stroke unit level was taken into account by multilevel modeling. In cases of missing data on the covariates, a separate category for missing data was added to the specific covariate. The requirements for linear regression were fulfilled in all analyses.

We performed a number of sensitivity analyses to evaluate the robustness of our findings. First, we replicated the analyses including only survivors (n = 2452). Second, the analyses were replicated without taking clustering by stroke unit into account and with robust cluster adjustment of the standard errors, respectively. Third, the analyses were done excluding patients for whom data on the covariates were missing (complete-case analyses). Fourth, instead of adjustment for Charlson Comorbidity Index we adjusted for myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, diabetes (type 1, 2), hemiplegia, moderate to severe renal disease, diabetes with end organ damage (type 1, 2), any tumor, leukemia, lymphoma, moderate to severe liver disease, metastatic solid tumor, and AIDS. Fifth, we replicated the analyses by stroke type, ie, hemorrhage and infarction. Sixth, we adjusted the results for medical complications during hospitalization. The results of the sensitivity analyses were compared with the results of the primary analyses (ie, analyses done by multilevel modeling) including patients who died during hospitalization, including separate categories for missing data on all covariates, including Charlson Comorbidity Index as a covariate, including both patients with infarction and hemorrhage, and excluding medical complications during hospitalization as covariates.

LOS was used as the dependent variable and to correct for the right skewness in this variable, a natural log (ln) transformation was used.[29] At reporting the final results, the estimates were transformed back into the original units by exponentiating the estimates and thereby, the ratios of the geometric mean of LOS were obtained.[29] Patients registered as hospitalized for 0 days (n = 6) were included in analyses as hospitalized for 0.5 days to enable the ln transformation of LOS, and the alteration was maintained in the results. Data were analyzed using Stata 9.2 (StataCorp LP, College Station, TX).

RESULTS

Table 1 summarizes the patient characteristics and the performance of the quality of care criteria for the 2636 patients admitted to stroke units. Median LOS was 13 days (25th and 75th percentiles: 7, 33), but LOS varied considerably between the stroke units (Table 1). For 9 out of the 12 quality of care criteria, missing data accounted for less than 5%. The criteria on nutritional risk assessment, constipation risk assessment, and venous thromboembolism prophylaxis had 9.3%, 36.0%, and 20.9% missing data, respectively (data not shown).

Table 2 presents the crude and adjusted relative LOS according to the quality of care criterion met. Meeting each quality of care criterion was associated with shorter LOS. Adjusted relative LOS ranged from 0.67 (95% confidence interval (CI): 0.61–0.73) for early mobilization to 0.87 (95% CI: 0.81–0.93) for early physiotherapy assessment, when adjustments were made for all 16 covariates. More than 95% of the patients were admitted to stroke units, received antiplatelet therapy, CT/MRI scan, physiotherapy and occupational therapy assessment, swallowing assessment, and were mobilized at some point during hospitalization but not necessarily within the defined time frame (data not shown). Therefore, the relative LOS for these criteria reflects the effect of early versus late intervention. Even so, the most prominent effects were seen for early mobilization (adjusted relative LOS: 0.67; 95% CI: 0.61–0.73) and early admission to a stroke unit (adjusted relative LOS: 0.71; 95% CI: 0.65–0.77).

As shown in Table 3, the association between meeting more quality of care criteria and LOS followed a dose-response effect. Patients who fulfilled between 75% and 100% of the criteria were hospitalized almost one-half as long as patients who fulfilled between 0% and 24% of the criteria when adjustments were made for all 16 covariates (adjusted relative LOS: 0.53, 95% CI: 0.48–0.59). The regression model accounted for 47.8% of the total variation in LOS. The variation between the stroke units accounted for 3.7% of the total variation.

The sensitivity analyses including only survivors produced results that were highly comparable with the results in Tables 2 and 3 (data not shown). The results varied between 0% and 6% from the results of the primary analyses. Second, analyses without adjustment for cluster by stroke unit and analyses with robust cluster adjustment of the standard errors produced results that were more extreme; eg, stronger associations, than the results in Tables 2 and 3 (data not shown). Third, handling missing data with complete-case analyses widened the 95% CIs because of the lower number of patients (data not shown). Still, the adjusted relative LOS were 0.90 or lower for all quality of care criteria except for the criteria on anticoagulant therapy (adjusted relative LOS: 0.92; 95% CI: 0.65–1.30) and venous thromboembolism prophylaxis (adjusted relative LOS: 0.91; 95% CI: 0.75–1.12). Fourth, including 19 specific comorbidities as covariates instead of Charlson Comorbidity Index produced results that were equivalent to the results in Tables 2 and 3 (data not shown). The results deviated between 0% and 5% from the results of the primary analyses. Fifth, when stratifying the analyses according to stroke type we found no substantial differences between the stratified and the pooled results (data not shown). The results varied between 0% and 13% from the results in Tables 2 and 3. Finally, including medical complications during hospitalization as covariates had only minor impact on the relative LOS (data not shown). The results deviated between 1% and 6% from the results in Tables 2 and 3.

DISCUSSION

This population-based follow-up study of patients with stroke who had been admitted to dedicated stroke units showed that higher quality of care, in accordance with early intensive evidence-based care, was associated with shorter LOS. The association, which remained even after careful adjustment for confounding factors, appeared to follow a dose-response pattern and was confirmed by all sensitivity analyses. Further, the association remained even when the reference group consisted only of patients who fulfilled the specific quality of care criteria later than 48 hours after hospital admission (ie, criteria on admission to a stroke unit, antiplatelet therapy, CT/MRI scan, physiotherapy and occupational therapy assessment, swallowing assessment and mobilization), emphasizing the importance of early intensive care).

The strengths of this study are its population-based design, the complete follow-up, and the detailed prospective data collection that enabled careful adjustment for a wide range of possible confounding factors. The results were adjusted for all known significant clinical predictors of LOS, including stroke severity upon admission.[3,30,31] Further, only patients eligible for care were included in analyses, minimizing the risk of confounding-by-indication. In light of the consistency of the results and the dose-response effect, it seems unlikely that the direction of the results can be attributed to unaccounted confounding alone. However, we cannot entirely exclude the possibility that our findings were influenced by unmeasured and residual confounding due to the nonrandomized study design. Because this study concerns internationally recommended clinical guidelines,[15,16,18] it is however not possibly to verify the results in a randomized, controlled, and blinded study for ethical reasons.

A potential limitation of the study is that the reliability of the DNIP data could have been limited by interobserver variability because the data are collected by different clinicians during routine clinical work. However, in DNIP extensive efforts are made to ensure the validity of the data.[12] Structured audit processes are regularly carried out on national, regional, and local bases to critically assess the quality of the data and results and provide continuous feedback to the hospital units.[12] Any misclassification was unlikely to be related to LOS due to the prospective design of the study and therefore would most likely have biased the relative LOS toward unity.

Based on an audit in DNIP, concerns have been raised about misclassification of the criteria on anticoagulant therapy which may affect the generalizability of this particular result. The result for anticoagulant therapy is however supported by the agreement with the results of the remaining quality of care criteria (Table 2). Including data from only 7 stroke units may also limit the generalizability of the study. However, only a minor part of the variation in LOS was caused by variation between the stroke units, and the distinct associations remained even after allowing for the variation between the stroke units by multilevel modeling. Therefore, the association between early intensive care and shorter LOS is likely to be independent of the underlying organizational variability between stroke units, and the study is likely to reflect current "real-life" clinical practice in Denmark and possibly also in other settings.

We are unaware of any studies that have addressed the association between specific care processes and LOS among patients with stroke. However, the results of this study are supported by other findings reported in the scientific literature. First, stroke unit care, characterized by early intensive care, tends to produce a modest reduction in LOS as compared with care in conventional wards.[32] However, which aspects of diagnosis, treatment, and care are responsible for the presumed positive effect on LOS are unclear.[32] This study suggests that early admission to a stroke unit is important from an economic perspective and thus, it supports the internationally recommended guidelines that patients with stroke should be admitted to stroke units in the acute phase of stroke.[15–18] Second, an Italian study showed that increased guideline compliance was associated with reduced hospital costs.[9] According to descriptive analyses, the study ascribed the cost savings to shorter LOS,[9] and although it did not directly assess the association between quality of care and LOS, the results of the Italian study strengthen the findings of our study. Third, an Australian study supports the prominent effect of early mobilization that was seen in our study. The study showed that early mobilization in addition to standard care incurs significant less cost at 3 and 12 months than standard care alone, largely attributable to less bed days in inpatient rehabilitation.[10]

The variation in LOS was only partly explained by the variables included in this study. According to the scientific literature, waiting time for admission to a nursing home and factors related to the culture and traditions in organizing the health care system are also associated with LOS and the costs of stroke care.[31,33–35] However, no studies have directly assessed the influence of these factors on the association between quality of care and LOS.

Still, the causal pathway between higher quality of care and shorter LOS remains to be clarified. The sensitivity analyses including medical complications during hospitalization as covariates indicated that only a minor part of the association was explained by prevention of medical complications.

Because higher quality of acute hospital care seems to be associated with reduced mortality among patients with stroke[6] as well as reduced LOS, it can be hypothesized that early intensive evidence-based hospital care is a cost-effective approach to treating patients with stroke. It has been shown specifically for mobilization that early intervention is likely to be cost-effective.[10] Because this study specifically addresses patients admitted to dedicated stroke units, it also acknowledges the existence of organizational variability between the stroke units and the possibility of improving the quality of care in these units. The question remains whether optimizing diagnosis, treatment, and care in stroke units is truly cost-effective. Several issues will need to be clarified before this question can be answered, including the costs of providing higher quality of care and the specific short- and long-term economic and health consequences.

In conclusion, this study demonstrated that higher quality of care, in accordance with early intensive evidence-based care, is associated with shorter LOS among patients with stroke who have been admitted to dedicated stroke units. In light of these findings, formal health economic evaluations of early intensive evidence-based hospital care for patients with stroke are warranted.

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Quality of early stroke care and hospital costs

Brief title: Quality of care and costs

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ABSTRACT

Objectives: The relationship between processes of care and hospital costs remains unclear. We therefore examined the association in a population-based cohort study.

Methods: We identified 5909 stroke patients who were admitted to stroke units in Aarhus County, Denmark, between 2005 and 2010. The examined processes of care included early admission to a stroke unit, early initiation of antiplatelet or anticoagulant therapy, early computed tomography/magnetic resonance imaging (CT/MRI) scan, early physiotherapy and occupational therapy assessment, early assessment of nutritional risk, constipation risk and of swallowing function, early mobilization, early intermittent catheterization, and early thromboembolism prophylaxis. Hospital costs were assessed for each patient based on the number of days spent in different in-hospital facilities using local hospital charges. Furthermore, potential bed-day savings were estimated using a daily base charge.

Results: The median hospital costs were 15340 USD (IQR: 6136-27443). The adjusted relative costs ranged from 0.65 (95% CI: 0.50-0.85) for early admission to a stroke unit to 0.97 (95% CI: 0.72-1.31) for early thromboembolism prophylaxis. The association between receiving more processes of care in the early phase of stroke and lower hospital costs followed a dose-response relationship. The potential bed-day savings per patient were 4553 USD (95% CI: 3980-5127) for patients who received 75-100% of the relevant processes of care compared with patients who received 0-24%.

Conclusions: Early care in agreement with key recommendations for the management of patients with stroke may be associated with substantial hospital savings.

INTRODUCTION

Stroke is a leading cause of death and disability worldwide.(1;2) The direct cost of stroke accounts for 2-4% of the total health care costs in developed countries, and more than half of the direct costs during the first year after stroke are attributable to the acute hospitalization and inpatient rehabilitation.(3-5)

Some individual management processes in the early phase of stroke have been linked with reduced risk of death and disability, including organized inpatient care in stroke units and early mobilization.(6;7) As a consequence, global efforts have been made to optimize the acute stroke care by implementing clinical guidelines for the early management of patients with stroke.(8;9) Furthermore, some studies suggest that urgent diagnostic work-up and treatment of patients with stroke may be associated with cost savings,(10-12) but a direct link between quality of early care and costs has not yet been established.(13) We have previously shown that early evidence-based care in agreement with consensus recommendations for the early management of patients with stroke was associated with shorter length of stay (LOS) in hospital among patients with stroke.(14) The aim of this study was to estimate the approximate hospital cost savings attributable to early evidence-based stroke care.

METHODS

In a population-based cohort study, we identified all patients with stroke who were admitted to a stroke unit in the former Aarhus County between 1 January 2005 and 31 December 2010 (n=5909). The study used prospectively collected data from Danish medical registries; including the Danish National Indicator Project (DNIP),(15) the Danish National Registry of

Patients,(16) and the Danish Civil Registration System.(17) The Danish National Health Service provides tax-supported health care for all inhabitants of Denmark, including free access to hospital care, and all medical emergencies, including stroke, are exclusively treated at public hospitals. All Danish citizens have been assigned a unique civil registration number since 1968 which is used in all health databases and permits unambiguous record linkage between them.

Data sources

DNIP was established in 2000 with the aim of documenting and improving the quality of care at national level for patients with specific diseases, including stroke (DNIP-stroke).(15) Project participation is mandatory for all Danish hospitals. Data are prospectively collected from the time of admission using a registration form with detailed written instructions. DNIP-stroke monitors whether several key recommendations for the early management of patients with stroke are followed, using evidence-based process indicators (Table 1).(8) In this article, the process indicators will also be referred to as processes of care. The DNIP-stroke database also contains data on socio-demographic and clinical characteristics. The Danish National Registry of Patients includes administrative data for all hospitalizations from 1977 onwards, including transfer dates to intensive care units (ICU) and rehabilitation wards, and discharge diagnoses coded according to the International Classification of Diseases (ICD).(16) The Danish Civil Registration System has registered all persons alive and living in Denmark since 1968 and includes daily updated information on vital status.(17)

Study population

Patients were identified from DNIP and included patients (≥ 18 years) who were hospitalized with acute stroke according to the WHO criteria. Only patients with intracerebral hemorrhage, cerebral infarction, or unspecified stroke were included. We identified 5916 patients who were first-time registered in the DNIP-stroke database and discharged from a stroke unit between 1 January 2005 and 31 December 2010. Patients who were registered as hospitalized for more than one year were excluded (n=7, 0.1 %), leaving a total of 5909 patients available for analyses.

Processes of care

An expert panel identified the process indicators taking into account the strength of evidence, the feasibility of collecting the required data in routine clinical settings, and the ability of the processes to reflect the multidisciplinary efforts involved in modern stroke care.(15) A time limit was defined for each process to capture the timeliness of care. The process indicators are defined in Table 1. Patients were classified as eligible or ineligible for the individual processes of care depending on whether the stroke team identified contraindications. Only patients who were considered eligible for the specific processes of care were included in the analyses.

Hospital Costs

Hospital costs were assessed individually for each patient from the hospital perspective based on the number of days spent in different medical facilities (acute care, ICU, and in-hospital rehabilitation), since previous studies have identified ICU utilization and LOS as main predictors of the total costs of in-hospital care among patients with stroke.(18-21) For patients who were admitted to ICU (≈3%), the days spent in ICU were subtracted from the days in acute care. For patients who received in-hospital rehabilitation in a distinct rehabilitation ward, the days in acute care covered the time from hospital admission until the date of transfer to the rehabilitation ward. Some patients received rehabilitation in a comprehensive stroke unit (i.e., covering both the acute hospitalization and in-hospital rehabilitation) and for these patients, the days in acute care was fixed at 12 days because the average transfer date to in-hospital rehabilitation in a distinct rehabilitation ward was 12 days after hospital admission. The total hospital costs were estimated by multiplying the bed-days in ICU, acute care, and rehabilitation by local hospital charges for 2010. The daily charges were 4127 USD for ICU, 1534 USD for acute care, and 821 USD for in-hospital rehabilitation. The cost of providing the specific processes of care was not included in the cost calculation. However, most patients received the processes of care at some time during hospitalization, but not necessarily in the early phase of stroke (Table 2). In addition, we calculated the potential bed-day cost savings by multiplying the saved bed-days per person with a daily base charge for nonmedical services, e.g., meals, cleaning, heating, water, and electricity (353 USD). All costs were converted into United States Dollar (USD) by applying the exchange rate on the 1st of January 2010 (1 DKK=0.193155 USD). We did not discount the costs because of the short time period analyzed.

Patient and hospital characteristics

Data regarding the following characteristics were collected at the time of hospital admission: age, sex, marital status, housing, alcohol intake, smoking habits, atrial fibrillation, hypertension, Charlson comorbidity index, Scandinavian Stroke Scale Score (SSS) upon admission, stroke subtype, calendar year, hospital university status, stroke unit setting, stroke unit volume, and treatment with thrombolysis (Supplementary Table 1). The Charlson comorbidity index covers 19 major disease categories and was computed for each patient based on ICD-10 discharge diagnoses from all hospitalizations since 1994, identified by linkage with the Danish National Registry of Patients. SSS was used to monitor the severity of stroke upon admission by evaluating the level of consciousness, eye movement, power in arm, hand, and leg, orientation, dysphasia, facial paresis, and gait.

Statistical Analysis

We calculated a total percentage score for the number of received processes of care within the time limit to reflect the overall quality of early stroke care. The score was calculated by dividing the total number of received processes of care within the time limit for each patient with the total number of processes of care that the patient was eligible for. The score was categorized into 0-24% (low-quality), 25-49% (medium/low-quality), 50-74% (medium/high-quality), and 75-100% (high-quality). The associations between the individual processes of care as well as the percentage score for quality of care and hospital costs were examined by linear regression. Adjustment was made for the aforementioned patient- and hospital characteristics; age and SSS were included as natural cubic splines. No adjustment was made for atrial fibrillation and stroke type in the analyses of antiplatelet therapy and anticoagulant therapy because only patients with ischemic stroke and without atrial fibrillation were eligible for antiplatelet therapy and only patients with ischemic stroke and atrial fibrillation were eligible for anticoagulant therapy. The results are reported as ratios between geometric mean of costs because a logarithm transformation was used to correct for the right skewness in hospital costs. The robustness of the results was evaluated in sensitivity analyses. First, we repeated all analyses restricted to patients who were discharged alive. Secondly, we performed the analyses with the daily charges for acute care, ICU and in-hospital rehabilitation, respectively, varied by 50% to evaluate how different assumptions about the average bed-day costs in each facility influenced the results. Third, we included medical complications during hospitalization as covariates, including pneumonia, urinary infection, decubitus, stroke related falls, deep vein thrombosis, pulmonary embolism, and constipation.

The potential bed-day cost savings were estimated by multiplying the LOS difference with a daily base charge. The LOS difference was calculated as the difference in the geometric mean LOS between patients who received the individual processes of care before or after the time limit. The LOS difference according to the total percentage score for quality of care was calculated with a score of 0-25% as reference. The uncertainty of the cost estimates was reflected by the upper and lower value of the confidence interval (CI).

Since a total of 34% of the patients had missing data on one or more of the patient characteristics, we used multiple imputation to impute the missing values assuming that data were missing at random (Stata command: ice). We imputed 5 datasets using the total percentage score for quality of care, the patient- and hospital characteristics, transfer to ICU and/or rehabilitation, death during hospitalization, a stroke unit identifier, and hospital costs. All of the analyses were performed with the imputed data and without (complete-case analysis). The analyses were corrected for clustering of patients within stroke units using robust estimates of the variance derived from the Huber/White/sandwich estimator of variance. Data were analyzed using Stata 10.1 (StataCorp LP, College Station, TX, USA). The study was approved by The Danish Data Protection Agency (J# 2007-41-1297).

RESULTS

The Supplementary Table 1 displays the patient and hospital characteristics according to the percentage of received processes of care. In general, patients who received a high quality of care tended to be younger, be male, live with someone, have less atrial fibrillation, less comorbid disease, and ischemic stroke. Patients admitted to neurologic stroke unit settings, stroke units with high case volume, and university hospitals also received a higher quality of care.

For most processes of care, Table 3 reflects the relative differences in costs for early versus delayed care, because the vast majority of the patients received the processes of care at some point during hospitalization, but not necessarily within the specified time limits (Table 2). The median hospital costs were 15340 USD (interquartile range (IQR): 6136-27443) and the median LOS was 10 days (IQR: 4-23). Receiving the processes of care within the time limits was associated with reduced hospital costs for most care processes; the adjusted relative costs ranged from 0.65 (95% CI: 0.50-0.85) for early admission to a stroke unit to 0.97 (95% CI: 0.72-1.31) for early thromboembolism prophylaxis (Table 3). All processes of care, except for early anticoagulant therapy and early thromboembolism prophylaxis, were also associated with potential bed-day cost savings. A distinct association was observed between early mobilization and reduced hospital costs (adjusted relative costs 0.70 (95% CI: 0.62-0.79)), and the estimated potential bed-day savings per patient were 3527 USD (95% CI: 2847-4207) for patients who were mobilized within the first day of hospitalization compared with patients who were mobilized at a later time during hospitalization.

Table 4 shows that the relationship between the percentage of received processes of care and hospital costs followed a dose-response relationship. The costs were approximately half among patients who received between 75% and 100% of the processes of care within the time limit compared with patients who received between 0% and 24% (adjusted relative costs: 0.49, 95% CI: 0.37-0.64). The potential bed-day savings per patient were 4553 USD (95% CI: 3980-5127) for patients who received 75-100% of the processes of care within the time limit compared with patients who received 0-24%.

The results were in general confirmed by all sensitivity analyses, including complete case analyses, analyses restricted to survivors, and analyses in which the hospital charges in each facility were varied by 50%. Adjustment for medical complications during hospitalization attenuated the results towards the null, but only to a limited extend.

DISCUSSION

We showed that early stroke care in agreement with key recommendations for the early management of patients with stroke may be associated with substantial savings in hospital costs.

To best of our knowledge, only one study has previously assessed the association between quality of stroke care and costs.(13) This Italian cohort study evaluated a rating of whether patients received 47 processes of care that were recommended by the American Heart Association, and showed that increased guideline compliance was associated with reduced hospital costs.(13) The hospital costs included the direct costs (i.e., diagnostic and intervention procedures, drugs and personnel) and non-direct costs (i.e., overheads and other general costs attributable to a patient's hospital stay). The cost savings were mainly ascribed to shorter LOS, but drug and personnel cost also remained lower for patients treated in accordance with guidelines, and the number of diagnostic procedures and specialist visits did not differ according to the level of guideline compliance.(13) Furthermore, the prominent association between early mobilization and reduced hospital costs was supported by an Australian study which showed that early mobilization in addition to standard care incurred significant less costs at 3 and 12 months compared with standard care alone.(12) The cost difference at 3 months was largely attributable to lesser inpatient rehabilitation costs amongst patients who received very early mobilization.(12) Our study suggests that early versus delayed admission to a stroke unit may be associated with hospital cost savings and it thus strengthens the internationally recommended guidelines that patients with stroke should be admitted to stroke units in the acute phase of stroke. (8;9) However, it is difficult to isolate the importance of individual management processes, because receiving the individual processes of care, e.g. early admission to a stroke unit, may correlate with optimized care in other areas.

A recent Japanese study investigated variations in costs during the early phase of stroke using fee-for-service cost data.(21) The study showed that the hospital costs are not necessarily concentrated to the early hospitalization phase as generally anticipated, and that differences in costs during the early phase of stroke are more influenced by ICU utilization and local management policies than by the clinical condition of the patients.(21) In addition, several studies have shown that the length of hospitalization determines a substantial part of the total costs of hospitalization among patients with stroke.(19;20) This argues that our cost data are sound with regard to reflecting differences in hospital costs. However, cost estimations based on average charges may overestimate the total costs of in-hospital care.(22) Consequently, we estimated the potential bed-day savings based on a daily base charge including only nonmedical services such as food, cleaning, and electricity. This should reflect the minimal potential bed-day savings since patients with stroke usually require clinical services, e.g., rehabilitation, throughout the complete hospitalization.

Our study indicates that some, but far from all of the association between receiving more processes of care and lower hospital costs was mediated through prevention of medical complications. However, the potential mediating role of medical complications in the association between increased guideline compliance and shorter length of stay has also been confirmed by other studies.(13;23;24) These findings may indicate that early evidence-based care provides further cost savings than suggested by our study due to improved clinical outcome and consequently, a reduced demand for future health care services.

Early evidence-based care in agreement with consensus recommendations for the early management of patients with stroke has also been linked with reduced risk of mortality and medical complications.(23;25) These findings imply that it may be cost-effective to provide early, evidence-based care because it improves health outcome while decreasing the costs. However, several issues will need to be clarified before more conclusive answers can be reached, including the specific costs of providing early evidence-based care, the exact short- and long-term economic consequences from a societal view (such as the rehabilitation costs after discharge and the cost of institutional care), and other short- and long-term health consequences (such as disability, quality of life, and patient satisfaction).

The main strengths of the study included the population-based design, the detailed and prospective data collection on individual patients, complete follow-up, and a large study population. This minimized the risk of selection and information bias. However, death during hospitalization shortened the observation period and thus, reduced the length of hospital stay. We evaluated the competing influence of death in a sensitivity analysis restricted to survivors and found no indication of bias. However, confounding is of concern because of the non-randomized design. We therefore adjusted for a wide range of factors known to be associated with hospital costs (e.g., age, marital status, and neurological symptoms upon admission) and adjusted for temporal trends, using calendar year, to account for potential changes over time in quality of care and length of hospital stay.(18;20) We also corrected for clustering of patients within stroke units, thereby taking into account unmeasured characteristics of the stroke units that may be associated with hospital cost.

In conclusion, our study highlights the importance of early evidence-based care among patients with stroke, and suggests that early care, and in particular early mobilization, may be associated with substantial hospital cost savings.

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Table 1. Definitions of the processes of care

Processes of care*	**Definition**	**Time limit**
Admission to a specialized stroke unit	Admission to a hospital department/unit that is exclusively or primarily dedicated to patients with stroke and characterized by multidisciplinary teams, a staff with a specific interest in stroke, involvement of relatives, and continuous education of the staff	Second day of hospitalization
Antiplatelet therapy initiated among patients with ischemic stroke without atrial fibrillation, or oral anticoagulant therapy initiated among patients with ischemic stroke and atrial fibrillation	Continuous use of the drugs and not merely a single dose	Antiplatelet therapy on second day of hospitalization or oral anticoagulant therapy on 14th day of hospitalization

CT/MRI scan		First day of hospitalization
Assessment by a physiotherapist and occupational therapist	Formal bed-side assessment of the patient's need for rehabilitation	Second day of hospitalization
Nutritional risk assessment	Assessment following the recommendations of the European Society for Parenteral and Enteral Nutrition	Second day of hospitalization
Assessment of swallowing function	Assessment according to the Gugging Swallowing Screen	First day of hospitalization
Assessment of constipation risk	Assessment upon admission by anamnesis	Second day of hospitalization
Early mobilization	Out-of-bed mobilization of the patient to a sitting position, standing or walking (unassisted or assisted), depending on the patient's general condition.	First day of hospitalization

Intermittent catheterization	Treatment with sterile intermittent catheterization because of urinary retention	Second day of hospitalization
Thromboembolism prophylaxis	Venous thromboprophylaxis with compression stockings and/or low molecular weight heparin (compression stockings only until 2006)	Second day of hospitalization

* All processes of care must be documented in the patient record

Table 2. Processes of care among 5909 patients with stroke, 2005-2009

Process of care (time limit, days)	**Eligible patients, n**	**Received on time, %**	**Received during hospitalization, %**	**Missing data, %**
Stroke unit (2)	5909	87.8	100	0
Antiplatelet therapy (2)	3749	87.6	99.4	0.7
Anticoagulant therapy (14)	497	74.9	83.7	6.3
CT/MRI scan (1)	5847	76.2	99.8	0.3
Physiotherapy (2)	5210	70.0	99.5	0.8
Occupational therapy (2)	5195	69.4	99.4	1.0
Nutritional assessment (2)	5227	74.0	96.6	4.4
Swallowing assessment (1)	5097	63.5	97.8	2.8
Constipation assessment (2)	4032	68.3	92.1	6.2
Mobilization (1)	5252	56.7	99.5	2.4
Sterile catheterization (2)	950	52.5	78.8	4.0
Thromboembolism prophylaxis (2)	1466	40.9	67.5	13.2

Table 3. Association between processes of care and hospital costs as well as potential bed-day savings

Process of care (time limit, days)	**Cost +/- process of care received, median (IQR)**	**Unadjusted cost ratio, (95 % CI)***	**Adjusted cost ratio, (95% CI)*†**	**LOS +/- process of care received, median (IQR)**	**Savings in bed-day cost (95% CI)***
Stroke unit (2)	23336 (15340-38941)/ 13806 (6136-25413)	0.52 (0.37-0.74)	0.65 (0.50-0.85)	9 (4-22)/18 (10-36)	3351 (2537-4165)
Antiplatelet therapy (2)	12272 (4602-23336)/ 19230 (10738-33192)	0.60 (0.42-0.85)	0.77 (0.66-0.90)	8 (3-19)/14 (7-30)	2169 (1295-3043)
Anticoagulant therapy (14)	18408 (9204-29907)/ 24158 (15340-40583)	0.72 (0.37-1.39)	0.84 (0.55-1.30)	13 (6-27)/20 (10-39)	2178 (-667-5024)
CT/MRI scan (1)	13806 (6136-26621)/ 18408 (9204-29907)	0.76 (0.59-0.98)	0.86 (0.72-1.02)	9 (4-23)/12 (6-26)	1099 (471-1727)

Physiotherapy (2)	15062 (7670-27443)/ 19230 (9204-33192)	0.74 (0.67-0.82)	0.80 (0.73-0.87)	10 (5-24)/14 (6-30)	1414 (1124-1703)
Occupational therapy (2)	13806 (6353-26621)/ 19230 (9204-33192)	0.73 (0.66-0.82)	0.80 (0.74-0.87)	10 (5-23)/14 (6/29)	1442 (1095-1789)
Nutritional assessment (2)	12272 (6136-24422)/ 21694 (12272-36477)	0.59 (0.50-0.69)	0.79 (0.69-0.91)	8 (4-21)/16 (8-34)	2489 (1917-3062)
Swallowing assessment (1)	12272 (4602-23336)/ 20872 (10738-34142)	0.59 (0.50-0.70)	0.78 (0.69-0.88)	8 (3-20)/15 (7-32)	2257 (1946-2569)
Constipation assessment (2)	12272 (4602-24979)/ 20872 (10738-39127)	0.61 (0.47-0.79)	0.83 (0.72-0.96)	9 (3-21)/16 (7-38)	2299 (547-4050)
Mobilization (1)	10738 (4602-20872)/ 21694 (12272-38398)	0.46 (0.32-0.67)	0.70 (0.62-0.79)	7 (3-16)/17 (8-37)	3527 (2847-4207)
Sterile catheterization (2)	25800 (13806-47154)/	0.89 (0.47-1.67)	0.85 (0.56-1.31)	21 (9-45)/20 (11-41)	1112 (-4266-6491)

	24979 (16874-43047)				
Thromboembolism prophylaxis (2)	25800 (12272-47527)/ 22515 (12272-43047)	1.07 (0.62-1.86)	0.97 (0.72-1.31)	22 (8-48)/17 (8-41)	-753 (-3725-2219)

* 95% CIs were calculated using robust estimates of the variance that allowed for clustering of patients within stroke units.

† Adjusted for age, gender, marital status, housing, profession, alcohol intake, smoking habits, Modified Rankin Scale Score prior to admission, atrial fibrillation (except for criteria on antiplatelet and anticoagulant therapy), hypertension, hyperlipidemia, Charlson comorbidity index, Scandinavian Stroke Scale Score upon admission, type of stroke (except for criteria on antiplatelet and anticoagulant therapy), year of hospitalization, stroke unit setting, stroke unit volume, hospital university status, and treatment with thrombolysis.

Table 4. Association between the percentage of received processes of care and hospital costs as well as potential bed-day savings

Processes received	**Cost, median (IQR)**	**Unadjusted cost ratio (95 % CI)***	**Adjusted cost ratio (95% CI)*†**	**LOS, median (IQR)**	**Savings in bed-day cost (95% CI)***
0%–24%	24979 (15340-40583)	Reference	Reference	20 (10-38)	Reference
25%-49%	21694 (13806-36477)	0 .86 (0.70-1.05)	0.87 (0.75-1.01)	17 (9-33)	1145 (22-2269)
50%-74%	18408 (9204-32370)	0.68 (0.55-0.83)	0.72 (0.59-0.88)	13 (6-30)	2543 (1645-3441)
75%-100%	10738 (4602-20872)	0.40 (0.30-0.52)	0.52 (0.39-0.70)	7 (3-16)	4553 (3980-5127)

* 95% CIs were calculated using robust estimates of the variance that allowed for clustering of patients within stroke units.

† Adjusted for age, gender, marital status, housing, profession, alcohol intake, smoking habits, Modified Rankin Scale Score prior to admission, atrial fibrillation, hypertension, hyperlipidemia, Charlson comorbidity index, Scandinavian Stroke Scale Score upon admission, type of stroke, year of hospitalization, stroke unit setting, stroke unit volume, hospital university status, and treatment with thrombolysis.

Supplementary Table 1. Descriptive characteristics of 5909 patients with stroke, 2005 – 2010

Characteristics	**Processes received: 0-24%**	**Processes received: 25-49%**	**Processes received: 50-74%**	**Processes received: 75-100%**
Age, mean (SD)	72.2 (14.3)	73.6 (12.7)	72.6 (12.9)	69.9 (13.3)
Gender, n (%)				
Male	212 (47.9)	344 (49.9)	798 (54.1)	1875 (56.8)
Female	231 (52.1)	345 (50.1)	678 (45.9)	1426 (43.2)
Marital status, n (%)				
Living with someone	200 (45.2)	324 (47.0)	742 (50.3)	1913 (58.0)
Living alone	229 (51.7)	340 (49.4)	667 (45.2)	1295 (39.2)
Other form of marital status	8 (1.8)	13 (1.9)	46 (3.1)	72 (2.2)
Missing data	6 (1.4)	12 (1.7)	21 (1.4)	21 (0.6)
Housing, n (%)				
Own home	376 (84.9)	609 (88.4)	1296 (87.8)	3023 (91.6)
Nursing home/institution	45 (10.2)	59 (8.6)	128 (8.7)	196 (5.9)
Other form of housing	8 (1.8)	10 (1.5)	25 (1.7)	36 (1.1)
Missing data	14 (3.2)	11 (1.6)	27 (1.8)	46 (1.4)
Profession, n (%)				
Employed/unemployed	72 (16.3)	92 (13.4)	248 (16.8)	777 (23.5)
Pensioner	348 (78.6)	555 (80.6)	1147 (77.7)	2426 (73.5)
Other form of profession	5 (1.1)	15 (2.2)	23 (1.6)	24 (0.7)
Missing data	18 (4.1)	27 (3.9)	58 (3.9)	74 (2.2)
Drinks/week, n (%)				
> 14 for women/> 21 for men	42 (9.5)	59 (8.6)	115 (7.8)	314 (9.5)
≤ 14 for women/≤ 21 for men	338 (76.3)	540 (78.4)	1173 (79.5)	2756 (83.5)
Missing data	63 (14.2)	90 (13.1)	188 (12.7)	231 (7.0)

Smoking habits, n (%)				
Never	132 (29.8)	214 (31.1)	414 (28.1)	904 (27.4)
Daily	145 (32.7)	220 (31.9)	500 (33.9)	1219 (36.9)
Occasionally	9 (2.0)	4 (0.6)	19 (1.3)	50 (1.5)
Former (> ½ year)	88 (19.9)	155 (22.5)	363 (24.6)	900 (27.3)
Missing data	69 (15.6)	96 (13.9)	180 (12.2)	228 (6.9)
Atrial fibrillation, n (%)				
Yes	118 (26.6)	158 (22.9)	308 (20.9)	587 (17.8)
No	309 (69.8)	521 (75.6)	1138 (77.1)	2663 (80.7)
Missing data	16 (3.6)	10 (1.5)	30 (2.0)	51 (1.5)
Hypertension, n (%)				
Yes	253 (57.1)	422 (61.3)	891 (60.4)	2067 (62.6)
No	170 (38.4)	245 (35.6)	541 (36.7)	1179 (35.7)
Missing data	20 (4.5)	22 (3.2)	44 (3.0)	55 (1.7)
Hyperlipidemia, n (%)				
Yes	189 (42.7)	314 (45.6)	771 (52.2)	2108 (63.9)
No	177 (40.0)	282 (40.9)	532 (36.0)	974 (29.5)
Missing data	77 (17.4)	93 (13.5)	173 (11.7)	219 (6.6)
Modified Rankin Scale, n (%)				
No symptoms at all	178 (40.2)	255 (37.0)	672 (45.5)	1712 (51.9)
No significant disability	57 (12.9)	109 (15.8)	201 (13.6)	478 (14.5)
Slight disability	57 (12.9)	91 (13.2)	170 (11.5)	444 (13.5)
Moderate disability	48 (10.8)	61 (8.9)	147 (10.0)	271 (8.2)
Moderately severe disability	26 (5.9)	47 (6.8)	85 (5.8)	150 (4.5)
Severe disability	2 (0.5)	6 (0.9)	13 (0.9)	20 (0.6)
Missing data	75 (16.9)	120 (17.4)	188 (12.7)	226 (6.9)
Comorbidity index, n (%)				
No comorbidity, 0	135 (30.5)	210 (30.5)	456 (30.9)	1168 (35.4)

Moderate comorbidity, 1-2	184 (41.5)	305 (44.3)	682 (46.2)	1446 (43.8)
Severe comorbidity, 3+	124 (28.0)	174 (25.3)	338 (22.9)	687 (20.8)
Stroke severity, n (%)				
Mild (45-58)	173 (39.1)	242 (35.1)	580 (39.3)	1792 (54.3)
Moderate (30-44)	79 (17.8)	127 (18.4)	314 (21.3)	661 (20.0)
Severe (15-29)	31 (7.0)	65 (9.4)	176 (11.9)	327 (9.9)
Very severe (0-14)	33 (7.5)	66 (9.6)	165 (11.2)	241 (16.3)
Missing data	127 (28.7)	189 (27.4)	241 (16.3)	239 (7.2)
Type of stroke, n (%)				
Ischemic	327 (73.8)	496 (72.0)	1089 (73.8)	2837 (85.9)
Intracerebral hemorrhage	69 (15.6)	78 (11.3)	210 (14.2)	325 (9.9)
Unspecified	47 (10.6)	115 (16.7)	177 (12.0)	139 (4.2)
Year of admission, n (%)				
2005	125 (28.2)	244 (35.41)	364 (24.66)	366 (11.09)
2006	97 (21.9)	135 (19.59)	296 (20.05)	566 (17.15)
2007	60 (13.5)	102 (14.80)	225 (15.24)	552 (16.72)
2008	54 (12.2)	69 (10.01)	201 (13.62)	566 (17.15)
2009	53 (12.0)	76 (11.03)	230 (15.58)	586 (17.75)
2010	54 (12.2)	63 (9.14)	160 (10.84)	665 (20.15)
Stroke unit setting, n (%)				
Neurological department	97 (21.9)	156 (22.6)	513 (34.8)	2192 (66.4)
Non-neurological department	346 (78.1)	533 (77.4)	963 (65.2)	1109 (33.6)
University hospital, n (%)				
Yes	188 (42.4)	291 (42.2)	720 (48.8)	2363 (71.6)
No	255 (57.6)	398 (57.8)	756 (51.2)	938 (28.4)
Stroke unit volume, n (%)				
0-236	116 (26.2)	220 (31.9)	412 (27.9)	564 (17.1)
237-715	327 (73.8)	469 (68.1)	1064 (72.1)	2737 (82.9)

Thrombolysis, n (%)				
Yes	8 (1.8)	23 (3.3)	98 (6.6)	496 (15.0)
No	435 (98.2)	666 (96.7)	1378 (93.4)	2805 (85.0)

Quality of Care and Patient Outcome in Stroke Units

Is Medical Specialty of Importance?

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Background: Specialized stroke unit care improves outcome in stroke patients. However, it is uncertain whether the units should be placed in a neurological or non-neurological (eg, internal medicine or geriatric) setting.

Objectives: To assess whether stroke unit setting (neurological/non-neurological) is associated with quality of care and outcome among patients with stroke, and whether these associations depend on the severity of comorbidity.

Methods: In a nationwide population-based follow-up study, we identified 45,521 patients admitted to stroke units in Denmark between 2003 and 2008. Outcomes were quality of care (whether patients received evidence-based processes of acute stroke care), mortality, length of stay, and readmission. Charlson comorbidity index was used to assess comorbidity, and comparisons were adjusted for patient and hospital characteristics.

Results: Patients admitted to stroke units in neurological settings had higher odds for early antiplatelet therapy (odds ratio, 1.68; 95% confidence interval, 1.10-2.56) and early computed tomographic scan or magnetic resonance imaging (odds ratio, 1.77; 95% confidence interval, 1.29-2.45) compared with patients in non-neurological settings. No other differences were found when studying quality of care and patient outcomes. However, patients with moderate comorbidity admitted to stroke units in neurological settings had higher odds for 1-year mortality, but comparisons across strata of comorbidity were not statistical significant.

Conclusions: Except for early antiplatelet therapy and early computed tomographic scan or magnetic resonance imaging, the medical setting was not associated with differences in processes of acute stroke care and patient outcome. No medical setting related differences were found according to comorbidity, although indications of a worse outcome in patients with moderate comorbidity in neurological settings warrant further investigation.

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The scientific literature in general suggests better outcomes with specialist care rather than generalists care for a broad range of diseases, and much of the available evidence shows that specialist physicians are able to deliver care of higher quality within the specific area of their specialty.[1] However, the studies have methodological shortcomings such as inadequate adjustment for patient case mix and practice environment.[1] Furthermore, the amount of evidence is limited, in particular in patients with multiple chronic conditions which traditionally is the strength and domain of generalists.[1] Among patients with stroke, several observational studies which were not restricted to stroke units found that patients with stroke are subjected to increased diagnostic testing and use of secondary medical prophylaxis when cared for by neurologists compared with other specialists.[2–6] A number of studies also showed that patients have a reduced risk of death when cared for by neurologists,[2,4,5,7–9] although this was not confirmed in other studies.[3,6,10] However, some studies question whether patients with comorbid disease profit by specialized care. Studies suggest that specialty settings may have inadequate coordination of care for coexisting diseases and that patients with comorbid disease may profit less by specialized treatment than healthier patients.[1,11,12]

On the basis of strong scientific evidence, there is broad consensus among experts that all patients with stroke should be admitted to specialized stroke units for diagnostic workup, treatment, care, and rehabilitation.[13–17] A specialized stroke unit is a hospital department or unit that is exclusively or primarily dedicated to patients with stroke and characterized by multidisciplinary team care.[18] However, several questions still remain with regard to the optimal organization of stroke units.[13,19] Stroke units may be established in department of neurology, geriatric medicine, or general medicine,[19] but the impact of stroke unit setting on quality of care and patient outcome is unknown.[7] Therefore, we examined whether stroke unit setting (neurological vs. non-neurological) is associated with quality of care and outcome among patients with stroke. Outcomes examined were 30-day and 1-year mortality, length of stay (LOS), 30-day readmission, and 30-day death or readmission. We also examined whether these associations depend on the severity of comorbid disease.

METHODS

This nationwide population-based follow-up study was based on prospectively collected data from Danish medical registries. 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 between databases.[20] The Danish National Health Service provides tax-supported health care for all inhabitants of Denmark, including free access to hospital care.[21] All medical emergencies, including stroke, are exclusively treated at public hospitals.

Data Sources

Patients were identified, and data were obtained from the Danish National Indicator Project (DNIP).[22] Information on vital status was acquired from the Civil Registration System,[20] and information on readmissions and comorbid disease was acquired from the Danish National Registry of Patients.[21]

DNIP was established in 2000 as a nationwide quality improvement project.[22] Participation is mandatory in all hospital units in Denmark treating patients with specific diseases, including stroke (DNIP-stroke).[22] The DNIP-stroke database encompasses data on patient characteristics, including sociodemographic and clinical data, and data on quality of care that indicates whether patients receive specific evidence-based processes of care in the acute phase of stroke. Data are, prospectively, collected on hospital admission as part of daily clinical work by the health care professionals taking care of the patients, using a standardized registration form with data specifications for each item. The Danish Civil Registration System has registered all persons alive and living in Denmark since 1968 and includes daily updated information on vital status.[20] Furthermore, the Danish National Registry of Patients has registered all patients admitted to Danish somatic hospitals since 1977.[21] The database includes information on date of admission and discharge, and discharge diagnoses for each hospitalization through life, classified according to the International Classification of Diseases (eighth revision until December 31, 1993 and 10th revision thereafter).

Patient Population

Patients, 18 years of age or older, are eligible for inclusion in the DNIP-stroke database if they are hospitalized with acute stroke according to the World Health Organization criteria, that is, rapidly developing symptoms and signs of focal or global neurological dysfunction of presumed vascular etiology lasting more than 24 hours or leading to death.[23] Only patients with intracerebral hemorrhage, cerebral infarction, or unspecified stroke are included. We identified 45,884 patients with acute stroke that were first-time registered in the DNIP-stroke database and discharged from a stroke unit in Denmark between January 13, 2003 and December 31, 2007. Patients who were lost to follow-up (n = 304, 0.7%) and patients who were registered as hospitalized for more than 1 year (n = 59, 0.1%) were excluded, leaving a total of 45,521 patients available for analyses. There were 41,876 patients available for the analyses of 30-day readmission and 30-day death or readmission since follow-up started on the day of hospital discharge, and 3645 patients died during hospitalization.

Stroke Unit Setting

Stroke unit setting refers to the medical department in which the stroke unit was established. The medical setting was classified according to the official Danish Classification of Danish Hospitals and Departments which uniquely identifies all Danish hospitals, hospital departments, and hospital units, and includes information on the primary medical specialty of each department/unit.[24] Accordingly, stroke units in neurological settings were located within departments of neurology, some of them also included neurosurgery and neurophysiology. Stroke units in non-neurological settings were located within departments of internal medicine, geriatrics, cardiology, hematology, nephrology, gastroenterology, endocrinology, oncology, respiratory medicine, infectious medicine, and rheumatology.

Processes of Acute Stroke Care

The processes of care covering the acute phase of stroke were identified by a national expert panel including physicians, nurses, physiotherapists, and occupational therapists based on a systematic literature review done in accordance with the methodology used by the Scottish Intercollegiate Guidelines Network.[22,25] The feasibility of collecting the required data in routine clinical settings and the ability of the processes to reflect the multidisciplinary efforts involved in modern stroke care were also considered.

A time frame was defined for each process to capture the timeliness of the interventions. The processes included admission to a stroke unit by the second day of hospitalization (yes/no), initiation of antiplatelet therapy by day 2 (yes/no), initiation of anticoagulant therapy by day 14 (yes/no), computed tomographic (CT) scan or magnetic resonance imaging (MRI) on the day of admission (yes/no), physiotherapy assessment by day 2 (yes/no), occupational therapy assessment by day 2 (yes/no), and assessment of nutritional risk by day 2 (yes/no). Furthermore, overall quality of care was measured as the proportion of received relevant processes of care (0 to 1). Initiation of antiplatelet and anticoagulant therapy was defined as continuous use of the drugs and not merely a single dose. Assessment by a physiotherapist and an occupational therapist was defined as formal bed-side assessment of the patient's need for rehabilitation, and assessment of nutritional risk was defined as assessment following the recommendations of the European Society for Parenteral and Enteral Nutrition.[26] Patients were classified as eligible or ineligible for each individual process of care depending on whether the stroke team identified contraindications, such as gastrointestinal bleeding precluding early antiplatelet therapy and rapid spontaneous recovery of motor symptoms making early assessment by a physiotherapist irrelevant. Only patients who were considered eligible for the specific process of care were included in the analyses on quality of care. No criteria for thrombolysis were defined, as only 334 patients (0.7%) were treated with tissue plasminogen activator during the study period.

Patient Outcomes

Patients were classified as either dead or alive by 30 days and 1 year after hospital admission. LOS was defined as the time span from hospital admission, or stroke occurrence if already hospitalized, until death or discharge. Any acute readmission with overnight stay (all causes) by 30 days after hospital discharge was considered a readmission.

Covariates

The following patient and hospital characteristics were included as covariates: age, sex, marital status (living with someone, living alone, other form of marital status), housing (own home, nursing home/institution, other form of housing), alcohol intake (women, $\leq$14/>14 drinks per week and men, $\leq$21/>21 drinks per week), smoking habits [daily, occasionally, former (>½ year since quitting), or never], atrial fibrillation, hypertension, Charlson comorbidity index (0, no comorbidity; 1 to 2, low comorbidity; $\geq$3, high comorbidity), Scandinavian stroke scale score (SSS) on admission (0 to 58), stroke subtype (infarction, intracerebral hemorrhage, unspecified stroke), calendar year (2003, 2004, 2005, 2006, 2007), hospital type (university vs. non-university), and departmental patient volume (average number of stroke patients per year). The Charlson comorbidity index quantifies the severity of comorbid disease in a summary score based on the presence or absence of 19 medical conditions.[27] We used an adapted version of the index that uses International Classification of Diseases codes by identifying all hospital diagnoses for each patient from 1994 onward in The Danish National Registry of Patients.[28] The Charlson comorbidity index is a useful score to adjust for comorbid disease in stroke outcome studies.[29] SSS is used to assess stroke severity on admission.[30,31] This scale is a validated and widely-used neurological stroke scale for evaluating the level of consciousness, eye movement, power in arm, hand, and leg, orientation, dysphasia, facial paresis, and gait. SSS can be assessed reliably either face to face or from routine hospital admission records.[32] The study was approved by the Danish Data Protection Agency (J# 2007-41-1297).

Statistical Analysis

Logistic regression was used to obtain odds ratios for the association between stroke unit setting and fulfillment of the individual processes of care, 30-day and 1-year mortality, 30-day readmission, and 30-day death or readmission. Linear regression was applied to examine the association between stroke unit setting and LOS and the proportion of received processes of care. To correct for the right skewness in LOS, a natural log transformation was used. At reporting the final results, the estimates were exponentiated back into the original units and thereby, the ratios between medians of LOS were obtained.[33] In multivariable analyses of patient outcomes, the associations were adjusted for the aforementioned patient (model 1) and patient plus hospital characteristics (model 2). Age, SSS, and departmental patient volume were included as natural cubic splines.[34] All associations were stratified for the severity of comorbid disease (Charlson comorbidity index: no 0, moderate 1 to 2, severe $\geq$3), and differences between the strata were examined using the Wald test.

In all the analyses, we corrected for clustering of patients within stroke units by using robust estimates of the variance derived from the Huber/White/sandwich estimator of variance.[35] Furthermore, as a total of 17,964 patients (39.5%) had missing data on one or more of the patient characteristics (Table 1), we used multiple imputation in all of the multivariable analyses to impute missing values assuming that data were missing at random (Stata command: ice).[36,37] We imputed 5 datasets using the following variables: age, sex, marital status, housing, alcohol, smoking habits, atrial fibrillation, hypertension, SSS, stroke subtype, calendar year, hospital university status, patient volume, stroke unit identifier, proportion of received processes of care, 1-year mortality, 30-day readmission, and an interaction term between stroke unit setting (neurological, non-neurological) and Charlson comorbidity index (0, 1 to 2, $\geq$3).

All of the analyses were performed both with and without the imputed data (complete case analysis). We also did an analysis of the association between stroke unit setting and patient outcome where we further adjusted for the proportion of received processes of care to assess whether differences in acute stroke care mediated any differences in patient outcome between patients admitted to stroke units in neurological and non-neurological settings. Data were analyzed using Stata 10.1 (StataCorp LP, College Station, TX).

RESULTS

Table 1 presents characteristics of the 45,521 patients with stroke according to stroke unit setting and severity of comorbid disease, and shows the original data before multiple imputation was applied. Data were obtained from 22 stroke units in neurological and 35 stroke units in non-neurological settings. In general, patients in neurological settings had a more favorable prognostic profile compared with patients in non-neurological settings. These patients tended to be younger, were less likely to have atrial fibrillation and hypertension, and had less severe strokes. However, more patients in neurological settings suffered from comorbid disease (ie, 69.6% of the patients in neurological settings had moderate or severe comorbid disease compared with 65.1% in non-neurological settings). Table 2 shows some key structural differences between the stroke units in neurological and non-neurological settings. Neurologists were only found in stroke units located in neurological settings, whereas the units located in non-neurological settings were served by general internists, cardiologists, geriatrists, and endocrinologists. Stroke units in neurological settings also tended to have a higher patient volume, easier access to intensive care unit facilities and were more often located at university hospitals compared with units in non-neurological settings.

Table 3 presents the association between stroke unit setting and processes of acute stroke care, assessed only among patients who were considered eligible for the specific process of care. Overall, patients in neurological settings received more processes of care than patients in non-neurological settings [unadjusted absolute difference in percentage points 5.08; 95% confidence interval (CI), 0.43-9.73]. Patients in neurological settings had higher odds of receiving early antiplatelet therapy [unadjusted odds ratio (OR), 1.68; 95% CI, 1.10-2.56] and early CT or MRI scan (unadjusted OR, 1.77; 95% CI, 1.29-2.45), but differences for the remaining 5 processes of care did not reach statistical significance. The association between stroke unit setting and the processes of care was unrelated to the severity of comorbid disease (data not shown).

According to Table 4, there was no overall association between stroke unit setting and patient outcomes. Patients in neurological settings suffering from moderate comorbid disease did have a statistically significant increased odds for 1-year mortality (adjusted OR, 1.18; 95% CI, 1.02-1.36), but

TABLE 1. Descriptive Characteristics of 45,521 Patients With Stroke According to Stroke Unit Setting (Neurological/Non-neurological) and Severity of Comorbid Disease

	Charlson Comorbidity Index = 0		Charlson Comorbidity Index = 1–2		Charlson Comorbidity Index = ≥ 3	
Characteristic	Neurological n = 9246	Non-neurological n = 5292	Neurological n = 14843	Non-neurological n = 6885	Neurological n = 6268	Non-neurological n = 2987
Age, mean (SD)	67.7 (14.3)	71.1 (13.0)	71.8 (13.2)	73.9 (11.9)	73.7 (11.6)	74.8 (10.9)
Sex, n (%)						
Male	4879 (52.8)	2663 (50.3)	7630 (51.4)	3576 (51.9)	3421 (54.6)	1607 (53.8)
Female	4367 (47.2)	2629 (49.7)	7213 (48.6)	3309 (48.1)	2847 (45.4)	1380 (46.2)
Marital status, n (%)						
Living with someone	5429 (58.7)	2906 (54.9)	7392 (49.8)	3426 (49.8)	2953 (47.1)	1387 (46.4)
Living alone	3348 (36.2)	2184 (41.3)	6299 (42.4)	3048 (44.3)	2715 (43.3)	1375 (46.0)
Other form of marital status	129 (1.4)	100 (1.9)	387 (2.6)	221 (3.2)	224 (3.6)	127 (4.3)
Missing data	340 (3.7)	102 (1.9)	765 (5.2)	190 (2.8)	376 (6.0)	98 (3.3)
Housing, n (%)						
Own home	8198 (88.7)	4755 (89.9)	12448 (83.9)	5899 (85.7)	5000 (79.8)	2460 (82.4)
Nursing home/institution	321 (3.5)	240 (4.5)	996 (6.7)	549 (8.0)	628 (10.0)	334 (11.2)
Other form of housing	179 (1.9)	99 (1.9)	338 (2.3)	132 (1.9)	150 (2.4)	55 (1.8)
Missing data	548 (5.9)	198 (3.7)	1061 (7.2)	305 (4.4)	490 (7.8)	138 (4.6)
Drinks/week, n (%)						
>14 for women and > 21 for men	742 (8.0)	338 (6.4)	1066 (7.2)	430 (6.3)	374 (6.0)	195 (6.5)
≤14 for women and ≤21 for men	7380 (79.8)	4235 (80.0)	11223 (75.6)	5091 (73.9)	4608 (73.5)	2124 (71.1)
Missing data	1124 (12.2)	719 (13.6)	2554 (17.2)	1364 (19.8)	1286 (20.5)	668 (22.4)
Smoking habits, n (%)						
Never	2970 (32.1)	1678 (31.7)	4212 (28.4)	1804 (26.2)	1590 (25.4)	702 (23.5)
Daily	3357 (36.3)	1854 (35.0)	4765 (32.1)	2213 (32.1)	1787 (28.5)	840 (28.1)
Occasionally	154 (1.7)	86 (1.6)	235 (1.6)	106 (1.5)	98 (1.6)	42 (1.4)
Former (>½ y)	1528 (16.5)	869 (16.4)	2681 (18.1)	1346 (19.6)	1293 (20.6)	704 (23.6)
Missing data	1237 (13.4)	805 (15.2)	2950 (19.9)	1416 (20.6)	1500 (23.9)	699 (23.4)
Atrial fibrillation, n (%)						
Yes	896 (9.7)	630 (11.9)	2336 (15.7)	1312 (19.1)	1351 (21.6)	745 (24.9)
No	7798 (84.3)	4462 (84.3)	11273 (76.0)	5249 (76.2)	4348 (69.4)	2097 (70.2)
Missing data	552 (6.0)	200 (3.8)	1234 (8.3)	324 (4.7)	569 (9.1)	145 (4.9)
Hypertension, n (%)						
Yes	3601 (39.0)	2396 (45.3)	6545 (44.1)	3316 (48.2)	3229 (51.5)	1624 (54.4)
No	5059 (54.7)	2621 (49.5)	6882 (46.4)	3079 (44.7)	2387 (38.1)	1154 (38.6)
Missing data	586 (6.3)	275 (5.2)	1416 (9.5)	490 (7.1)	652 (10.4)	209 (7.0)
Scandinavian stroke scale, n (%)						
Mild (45-58)	5683 (61.5)	3172 (59.9)	6897 (46.5)	3274 (47.6)	2470 (39.4)	1208 (40.4)
Moderate (30-44)	1211 (13.1)	874 (16.5)	2428 (16.4)	1434 (20.8)	1139 (18.2)	687 (23.0)
Severe (15-29)	549 (5.9)	457 (8.6)	1374 (9.3)	750 (10.9)	670 (10.7)	361 (12.1)
Very severe (0-14)	485 (5.3)	356 (6.7)	1510 (10.2)	780 (11.3)	747 (11.9)	380 (12.7)
Missing data	1318 (14.3)	433 (8.2)	2634 (17.8)	647 (9.4)	1242 (19.8)	351 (11.8)
Type of stroke, n (%)						
Ischemic	6600 (71.4)	3806 (71.9)	10165 (68.5)	4695 (68.2)	4441 (70.9)	2086 (69.8)
Intracerebral hemorrhage	698 (7.6)	474 (9.0)	1816 (12.2)	767 (11.1)	640 (10.2)	279 (9.3)
Unspecified	1948 (21.1)	1012 (19.1)	2862 (19.3)	1423 (20.7)	1187 (18.9)	622 (20.8)
Year of admission, n (%)						
2003	1290 (14.0)	890 (16.8)	2277 (15.3)	1374 (20.0)	839 (13.4)	504 (16.9)
2004	1695 (18.3)	1167 (22.1)	3110 (21.0)	1534 (22.3)	1223 (19.5)	670 (22.4)
2005	1846 (20.0)	1206 (22.8)	2944 (19.8)	1502 (21.8)	1278 (20.4)	690 (23.1)
2006	2252 (24.4)	1073 (20.3)	3356 (22.6)	1305 (19.0)	1531 (24.4)	559 (18.7)
2007	2163 (23.4)	956 (18.1)	3156 (21.3)	1170 (17.0)	1397 (22.3)	564 (18.9)

TABLE 2. Descriptive Characteristics of Stroke Units in Neurological and Non-neurological Settings

Characteristics	Neurological Setting	Non-neurological Setting
Senior neurologist, n (%)		
Yes	22 (100)	—
No	—	35 (100)
Stroke patients/year*	365 (298-539)	203 (118–282)
ICU in hospital, n (%)		
Yes	22 (100)	21 (60.0)
No	—	14 (40.0)
University hospital, n (%)		
Yes	12 (54.5)	9 (25.7)
No	10 (45.5)	26 (74.3)

*Median (interquartile range).
ICU indicates intensive care unit.

the differences between the individual strata of comorbid disease did not reach statistical significance. Table 4 also shows that adjustment for patient characteristics (model 1) and hospital characteristics (model 2) had considerable impact in the analyses on mortality and LOS, whereas the odds estimates remained virtually unchanged when adjustment was also made for the proportion of received processes of care (data not shown). Complete case analysis (without the imputed data) yielded, in general, the same results as shown in Table 4 and showed no apparent association between stroke unit setting and patient outcome (data not shown).

DISCUSSION

We found no evidence that stroke units in neurological and non-neurological settings overall differ with regard to a broad range of essential processes of acute stroke care and patient outcome. Neurological stroke unit setting was, however, positively related to receiving antiplatelet therapy and CT or MRI scan in the early phase of stroke.

Stroke care requires expertize from several medical fields, including neurology, vascular medicine, internal medicine, and rehabilitation medicine, and it has been widely debated who should treat patients with stroke.[38] Our study suggests that stroke units encompass the required medical expertize since we found no difference in several essential processes of acute stroke care and patient outcome between neurological and non-neurological stroke unit settings. Stroke units are characterized by intensive stroke specialization through continuous education of the staff and a well-established clinical practice, including the use of CT or MRI scan and multidisciplinary rehabilitation,[18,19] and these characteristics may be among the components that diminish the potential basic differences between the primary medical specialties in stroke units. Nevertheless, this study did indicate that not only clinical and sociodemographic characteristics, but also health service characteristics may be important in relation to the prognosis of stroke, as adjustment for hospital characteristics, including departmental patient volume and hospital university status, had considerable impact in the analyses on mortality and LOS.

Strengths and Limitations

The main strength of this study lies in its prospective population-based design with almost complete follow-up and therefore, low risk of selection and information bias. By using multiple imputation to impute missing values, we also limited the risk of bias from missing data,[37] and our results were further confirmed by a complete case analysis.

As this is an observational study, results may be affected by unaccounted confounding or residual confounding. However, several precautions were taken to minimize the impact of possible confounding. We adjusted for a wide range of known prognostic factors, including age, atrial fibrillation, and initial stroke severity.[39–42] Furthermore, only patients considered eligible for care were included in analyses of the individual processes of care, minimizing the risk of confounding by indication. We also corrected for clustering of patients within stroke units, thereby taking into account unmeasured characteristics of the stroke units that may be associated with outcome. LOS represented a specific problem, as both acute stroke units and comprehensive

TABLE 3. Stroke Unit Setting (Neurological/Non-neurological) and Processes of Acute Stroke Care

Process of Care	Neurological Setting	Relevant Patients, n*	Process of Care Received, %	Unadjusted OR (95% CI)†
Stroke unit (by day 2)	Yes	30352	91.9	1.47 (0.84–2.59)
	No	15161	88.5	
Antiplatelet therapy (by day 2)	Yes	19223	84.3	1.68 (1.10–2.56)
	No	9876	76.1	
Anticoagulant therapy (by day 14)	Yes	2341	57.8	0.73 (0.46–1.18)
	No	1481	65.1	
CT/MRI scan (by day 1)	Yes	29286	56.8	1.77 (1.29–2.45)
	No	14891	42.5	
Physiotherapy (by day 2)	Yes	23939	60.0	0.89 (0.65–1.23)
	No	13580	62.7	
Occupational therapy (by day 2)	Yes	24104	54.7	0.86 (0.66–1.11)
	No	13511	58.4	
Nutritional assessment (by day 2)	Yes	21520	61.8	1.35 (0.97–1.86)
	No	11796	54.6	

*Patients who were considered eligible for the specific process of care.
†95% CIs were calculated using robust estimates of the variance that allowed for clustering of patients within stroke units.
CI indicates confidence interval; CT, computed tomography; MRI, magnetic resonance imaging; OR, odds ratio.

TABLE 4. Stroke Unit Setting (Neurological/Non-neurological) and Patient Outcome According to the Severity of Comorbid Disease

	Neurological Setting	Study Population, n	Events, *P**	Unadjusted Ratio (95% CI)†	Adjusted Ratio (95% CI), Model 1† ‡	Adjusted Ratio (95% CI), Model 2† §	*P*
30-day mortality	Yes	30357	9.7	0.96 (0.82–1.14)	1.00 (0.85–1.18)	1.12 (0.89–1.40)	
	No	15164	10.0				
Charlson comorbidity index = 0	Yes	9246	4.7	0.79 (0.62–1.01)	0.97 (0.76–1.23)	1.06 (0.81–1.40)	0.38
	No	5292	5.9				
Charlson comorbidity index = 1-2	Yes	14843	10.3	0.98 (0.80–1.19)	1.06 (0.88–1.29)	1.19 (0.92–1.54)	
	No	6885	10.5				
Charlson comorbidity index = ≥ 3	Yes	6268	15.6	0.95 (0.79–1.14)	0.93 (0.77–1.12)	1.04 (0.82–1.32)	
	No	2987	16.3				
1-year mortality	Yes	30357	20.9	0.95 (0.84–1.07)	1.02 (0.92–1.13)	1.10 (0.98–1.24)	
	No	15164	21.8				
Charlson comorbidity index = 0	Yes	9246	10.4	0.77 (0.65–0.92)	0.94 (0.81–1.09)	1.01 (0.87–1.18)	0.16
	No	5292	13.0				
Charlson comorbidity index = 1-2	Yes	14843	21.9	0.96 (0.84–1.08)	1.09 (0.96–1.23)	1.18 (1.02–1.36)	
	No	6885	22.7				
Charlson comorbidity index = ≥ 3	Yes	6268	34.1	0.94 (0.81–1.08)	0.97 (0.83–1.12)	1.04 (0.89–1.22)	
	No	2987	35.6				
Length of stay	Yes	30357	—	0.68 (0.51–0.89)	0.71 (0.55–0.91)	0.86 (0.64–1.15)	
	No	15164	—				
Charlson comorbidity index = 0	Yes	9246	—	0.62 (0.49–0.80)	0.68 (0.54–0.85)	0.85 (0.66–1.10)	0.32
	No	5292	—				
Charlson comorbidity index = 1-2	Yes	14843	—	0.69 (0.51–0.92)	0.71 (0.55–0.93)	0.86 (0.63–1.17)	
	No	6885	—				
Charlson comorbidity index = ≥ 3	Yes	6268	—	0.71 (0.52–0.98)	0.74 (0.55–0.99)	0.87 (0.64–1.20)	
	No	2987	—				
30-day readmission	Yes	27986	8.5	1.04 (0.90–1.21)	1.02 (0.88–1.18)	1.03 (0.91–1.15)	
	No	13890	8.2				
Charlson comorbidity index = 0	Yes	8893	5.2	0.91 (0.74–1.12)	0.91 (0.75–1.11)	0.91 (0.77–1.07)	0.11
	No	5026	5.6				
Charlson comorbidity index = 1-2	Yes	13613	9.2	1.07 (0.90–1.28)	1.44 (1.20–1.72)	1.08 (0.94–1.24)	
	No	6289	8.6				
Charlson comorbidity index = ≥ 3	Yes	5480	12.4	1.01 (0.84–1.22)	1.01 (0.85–1.21)	1.02 (0.86–1.22)	
	No	2575	12.3				
30-day death or readmission	Yes	27986	11.8	1.02 (0.89–1.17)	1.03 (0.91–1.16)	1.04 (0.93–1.16)	
	No	13890	11.6				
Charlson comorbidity index = 0	Yes	8893	6.7	0.88 (0.73–1.06)	0.92 (0.77–1.09)	0.92 (0.78–1.09)	0.13
	No	5026	7.6				
Charlson comorbidity index = 1-2	Yes	13613	12.6	1.04 (0.89–1.21)	1.08 (0.93–1.25)	1.10 (0.95–1.26)	
	No	6289	12.2				
Charlson comorbidity index = ≥ 3	Yes	5480	17.9	1.01 (0.85–1.19)	1.03 (0.88–1.20)	1.04 (0.90–1.21)	
	No	2575	17.8				

*The median length of stay was 6 days (interquartile range, 3 to 14) in neurological settings and 10 days (interquartile range, 5 to 22) in non-neurological settings.
†95% CIs were calculated using robust estimates of the variance that allowed for clustering of patients within stroke units.
‡Ratio between medians if length of stay, and odds ratio otherwise. Adjusted for age, sex, marital status, housing, alcohol intake, smoking habits, Charlson comorbidity index (except for the stratified analyses), atrial fibrillation, hypertension, Scandinavian stroke scale score by admission, stroke subtype, and calendar year.
§Further adjusted for hospital university status and departmental patient volume in addition to model 1.
CI indicates confidence interval.

stroke units (ie, units covering both the acute and rehabilitation phase) were included in the study. Some inherent variation in LOS between the departments could therefore be expected, but this variation was found among units in both neurological and non-neurological settings and was therefore unlikely to explain the relative differences in LOS. Another potential weakness of the study lies in the risk of misclassification because data were collected in routine clinical settings. However, DNIP regularly carries out structured audit processes on a national, regional, and local basis to ensure the validity of the data.[22]

Comparison With Other Studies

To best of our knowledge, this study is the first to specifically address the association between stroke unit setting and timely evidence-based care. However, our findings are in accordance with a number of follow-up studies, not restricted to stroke units. These studies found that stroke patients seen by neurologists are more likely than those not seen by neurologists to receive diagnostic tests, including MRI scan, and secondary medical prophylaxis, including ticlopidine, warfarin, heparin, and heparinoid.[2–6,12] Furthermore, a number of studies found that stroke patients have better survival when cared for by neurologists compared with other specialists,[2,4,5,8,9] but not all studies confirm such association.[3,6,10] Only 1 other study has specifically addressed the relationship between the medical specialty in stroke units and patient outcome.[7] This Italian follow-up study of 11,572 patients with acute stroke found no difference in the risk of death or disability whether or not stroke units had neurological beds only (OR, 0.88; 95% CI, 0.55-1.39), but the study did find a reduced risk of death and disability in conventional wards with only neurological beds (the wards had no beds or staff dedicated to stroke patients) (OR, 0.64; 95% CI, 0.55-0.75). The study was limited by including only 31 stroke units and making incomplete or no adjustment for potential important confounding factors, such as stroke severity and comorbid disease. Even so, our study supports their findings, that is, that stroke unit setting has no overall association with patient outcome.

Only few other studies have focused on the relationship between specialization of hospital care and comorbid disease, and these studies suggest that patients with comorbid disease profit less by specialized treatment than healthier patients.[2,11,12] A study on patients undergoing coronary artery bypass graft surgery showed that patients with comorbid disease experienced worse 30-day post discharge mortality when treated at cardiac specialty hospitals compared with patients treated at less specialized hospitals.[11] In contrast, there was no association between specialization and mortality among healthier patients. Furthermore, a study on patients with stroke showed that patients with atrial fibrillation had worse survival when cared for on neurology services compared with general services, whereas patients without atrial fibrillation had better survival when cared for on neurology services.[12] Another study on stroke patients showed that patients in neurology services compared with general services had increased risk of rehospitalization with heart disease.[2] Although we were unable to show any statistically significant differences between patients with no, moderate, and severe comorbid disease, our results did indicate a potentially worse outcome among patients with moderate comorbid disease. These results may be chance findings, but it cannot be ruled out that stroke patients with moderate comorbid disease are not treated optimally in specialized neurological settings. Further studies appear warranted to further clarify this issue.

In conclusion, neurological stroke unit setting was positively related to receiving antiplatelet therapy and CT or MRI scan in the early phase of stroke. The medical setting was, however, not associated with any other substantial differences in essential processes of acute stroke care and patient outcome. No medical setting related differences were found according to comorbidity, but indications of a worse outcome among patients with moderate comorbid disease treated in neurological stroke unit settings warrant further investigation.

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Higher stroke unit volume associated with improved quality of early stroke care and reduced length of stay

Cover title: Higher volume, improved care, and bed-day savings

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ABSTRACT

Background and Purpose: Specialized stroke unit care improves outcome among stroke patients, but it is unclear whether there are any scale advantages from treating a larger number of patients. We examined whether the case volume in stroke units was associated with quality of early stroke care, mortality, and hospital bed-day use.

Methods: In a nationwide population-based cohort study, we identified 63,995 patients admitted to stroke units in Denmark between 2003 and 2009. Data on exposure, outcome, and covariates were collected prospectively. Comparisons were clustered within stroke units, and adjusted for patient- and hospital characteristics.

Results: Patients who were admitted to high volume stroke units received more processes of care in the early phase of stroke compared with patients in low volume stroke units (unadjusted difference 9.84 percentage points (95% CI 3.98-15.70)). High stroke unit volume was also associated with shorter length of the initial hospital stay (adjusted ratio 0.49 (95% CI 0.41-0.59)) and reduced bed-day use in the first year after stroke (adjusted ratio 0.79 (95% CI 0.70-0.87)). No association between volume and mortality was found.

Conclusions: Patients admitted to high volume stroke units received a higher quality of early stroke care and spent fewer days in hospital compared with patients in low volume units. We observed no association between volume and mortality.

INTRODUCTION

A key element in modern stroke care is in-hospital care in dedicated stroke units,[1, 2] but it is still unclear how to organize stroke units optimally.[1] Higher volume of health services has been linked with better clinical outcomes across a variety diseases, in particular in patients undergoing invasive procedures.[3] In addition, hospitals, and in particular small-scale hospitals, may experience economies of scale and thus obtain reduced average cost per patient as volume increases.[4-6] Higher case volume has also been linked with lower mortality[7-13] and lower costs among patients with stroke;[14] and to our knowledge, no studies have linked high volume with unfavorable outcomes.[15-19] However, the mechanisms underlying these associations are complex and uncertain. Little is, e.g., known about potential differences in stroke care between high and low volume providers.[19-21] Therefore, we examined whether the annual case volume in stroke units is associated with the quality of early stroke care, 30-day and one-year mortality, length of the initial hospital stay (LOS), and hospital bed-day use in the first year after stroke.

METHODS

This nationwide population-based cohort study was based on prospectively collected data from Danish medical registries. Since 1968, all Danish residents have been assigned a unique civil registration number which is used in all health databases and allows for unambiguous record linkage between databases.[22] The Danish healthcare system provides free access to hospital care for all Danish residents.[23] All medical emergencies, including stroke, are exclusively admitted to public hospitals.

Data sources

Data were obtained from the Danish National Indicator Project (DNIP),[24] the Civil Registration System,[22] and the Danish National Registry of Patients.[23] DNIP was established in 2000 with the aim of documenting and improving the quality of care for eight diseases at national level, including stroke (DNIP-stroke). Project participation is mandatory for all hospital units treating patients with stroke.[24] The DNIP-stroke database contains information on whether several key recommendations for the early management of patients with stroke are followed, using evidence-based quality of care indicators.[2] The database also contains socio-demographic and clinical data. Data is prospectively collected upon hospital admission using a standardized form with detailed instructions. The Danish Civil Registration System contains information on all Danish residents from 1968 onwards and includes daily updated information on vital status.[22] The Danish National Registry of Patients holds records of all patients admitted to Danish somatic hospitals since 1977 and contains data from all hospitalizations, including discharge diagnoses coded according to the International Classification of Diseases (ICD).[23]

Study population

All patients (≥ 18 years) hospitalized with acute stroke (intracerebral hemorrhage, cerebral infarction, or unspecified stroke) according to the WHO criteria[25] are eligible for inclusion in the DNIP-stroke database. We identified 64,470 Danish citizens with stroke who had a first-time registration in the DNIP-stroke database and were discharged from a stroke unit in Denmark (61 stroke units) in the period 13th January 2003 to 31st December 2009. We excluded patients who were lost to follow-up (n=475, 0.7%), leaving a total of 63,995 patients available for analyses of whom 5,031 patients died during the first hospitalization.

Annual case volume in stroke units

Annual case volume was defined as the average number of stroke patients treated in a stroke unit per year from 2003 to 2009. A stroke unit was defined as described in Table 1.

Processes of early stroke care

In DNIP, the processes of care were identified by a national expert panel taking into account the strength of evidence, the multidisciplinary efforts in modern stroke care, and the feasibility of collecting the data in routine clinical settings.[24, 26] A time limit was defined for each process to capture the timeliness of the interventions (Table 1). Patients were classified as eligible or ineligible for the individual processes of care depending on whether the stroke team identified contraindications. We calculated a total percentage score of received processes of care within the time limit to reflect the overall quality of early stroke care by dividing the total number of received processes of care within the time limit for each patient with the total number of processes of care that the patient was eligible for. Only patients who were considered eligible for the specific processes of care were included in the analyses.

Outcomes

Follow-up on mortality started on the day of hospital admission and ended after either 30 days or one year. LOS was defined as the time span from hospital admission, or stroke occurrence if already hospitalized, until death or discharge. One-year bed-day use included every hospitalization with overnight stay (all-causes) during the first year after stroke.

Covariates

Data were collected on age, sex, marital status, type of housing, alcohol intake, smoking habits, atrial fibrillation, hypertension, Charlson comorbidity score[27], Scandinavian Stroke Scale score[28] (SSS) upon admission, stroke subtype, calendar year, hospital university status, and stroke unit setting (please see http://stroke.ahajournals.org.). The Charlson comorbidity score covers 19 diseases/conditions and was calculated by identifying the ICD-10 diagnoses for each patient from 1994 onwards in The Danish National Registry of Patients.[27]

Statistical Analyses

The relationship between volume and outcomes was examined using spline curves (natural cubic spline of volume with five knots).[29] We created volume quartiles of approximate equal numbers of patients (0-231, 232-330, 331-498, and 499-915 patients/year), and performed the analyses with logistic regression (the individual processes of care and mortality) and linear regression (total percentage score for quality of care, LOS, and one-year bed-day use). We used a natural log transformation to correct for the right skewness in LOS and one-year bed-day use, and the results are reported as ratios between geometric means.[30] The associations between volume and mortality, LOS, and one-year bed-day use, respectively, were adjusted for the aforementioned patient characteristics (model 1), plus hospital characteristics (model 2), plus the total percentage score for quality of care (model 3). Age and SSS were included as natural cubic splines.[29]

A total of 24,340 patients had missing data on one or more of the covariates (please see the supplemental table S1, available at http://stroke.ahajournals.org). We used multiple imputation to impute the missing values assuming that data was missing at random (Stata command: ice).[31, 32] We created five datasets based on the aforementioned covariates, a stroke unit identifier, the total percentage score for quality of care, one-year mortality, and one-year bed-day use. All 95% confidence intervals (CI) were corrected for clustering of patients within stroke units using robust estimates of the variance derived from the Huber/White/sandwich estimator of variance.[33]

In order to evaluate the robustness of our findings, we also performed the analyses restricted to patients without missing data (complete case analysis). Furthermore, the analyses on LOS and one-year bed-day use were repeated after excluding patients who died during hospitalization or during the first year after stroke, respectively. Finally, the analyses were stratified according to age, stroke severity, and comorbidity. Data were analyzed with Stata 10.1 (StataCorp LP, College Station, TX, USA).[31] The study was approved by The Danish Data Protection Agency (J# 2007-41-1297).

RESULTS

Descriptive data on the 63,995 patients are presented in the supplemental table S1 (please see http://stroke.ahajournals.org). Patients in high volume stroke units tended to be younger, have less atrial fibrillation and hypertension, and less severe neurological symptoms upon admission compared with patients in low volume stroke units. Furthermore, stroke units with high case volume were more often located in neurological departments and university hospitals.

Figure 1 showed that there were no essential non-linear relationships between volume and the percentage score for quality of care, mortality, and bed-day use. Patients who were admitted to high volume stroke units received more processes of care in the early phase of stroke compared with patients in low volume stroke units (0-231 patients/year (reference); 232-330;

331-498; and 499-915: unadjusted difference in percentage points 3.13 (95 % CI -2.03-8.29); 8.64 (95 % CI 2.62-14.67); and 9.84 (95 % CI 3.98-15.70)). Patients had substantially higher odds of being admitted early to high volume stroke units compared with low volume stroke units (unadjusted odds ratio 3.44 (95 % CI 1.69-7.00)). Furthermore, patients in high volume stroke units had statistically significantly higher odds of receiving early antiplatelet therapy, early CT/MRI scan, early occupational therapy assessment, and early nutritional assessment (Table 2).

Higher case volume was consistently associated with shorter initial LOS (adjusted ratio 0.49 (95% CI 0.41-0.59)) and with reduced bed-day use in the first year after stroke when focusing on all-cause hospitalizations (adjusted ratio 0.79 (95% CI 0.70-0.87)) (Table 3). There was no statistically significant association between volume and 30-day or one-year mortality.

Complete case analyses provided results very similar to the analyses including the entire study population, except for higher odds of death among patients in high volume stroke units compared with patients in low volume stroke units (30-day and one-year mortality: adjusted ratio 1.26 (95% CI 1.03-1. 55) and 1.13 (95% CI 0.97-1.32)). The results for bed-day use were also robust when excluding patients who died during the initial hospitalization (LOS) or during the first year after stroke (one-year bed-day use) (data not shown). We found no indications of interaction when stratifying the analyses according to age, stroke severity, and severity of comorbidity (data not shown).

DISCUSSION

Our results showed that higher annual case volume in stroke units was associated with higher quality of early stroke care and reduced hospital bed-day use. These results may imply that high volume stroke units provide better quality of early care at lower costs, because inpatient care accounts for a substantial part of the health care costs after stroke.[34, 35]

Considering the non-randomized design, our results may be influenced by residual confounding due to the use of crude variables (e.g., using a summary score for comorbidity) or unaccounted confounding (e.g., pre-stroke disability) although we adjusted for important prognostic factors such as age and initial stroke severity.[13, 36, 37] Furthermore, an association between higher volume and shorter initial LOS may originate from a reverse relationship because early discharge results in free capacity for more patients. Nevertheless, we also observed a clear association between higher volume and reduced hospital bed-day use when focusing on all-cause hospitalizations in the first year after stroke which may substantiate a true link between higher volume and shorter length of the initial hospital stay and/or lower risk of readmissions.

Missing from most research is an exploration of the mechanisms through which volume influences outcome.[3] According to our knowledge, only three existing studies have compared quality of stroke care between high and low volume institutions. One study (not restricted to stroke units) showed that higher hospital bed size was associated with better quality of stroke care,[21] while other studies found no direct link between volume and quality of care.[17, 18] In our study, adjusting for the percentage of received processes of care had no major influence on the results, suggesting that other factors may also contribute to the reduced LOS and one-year bed-day use in high volume stroke units. There may be several underlying mechanisms that can explain the observed associations, including a learning effect and more efficient working procedures in high volume institutions.[5, 6]

Interestingly, we did not find a link between higher volume and lower mortality. Unlike most previous studies,[7-12, 14, 16-18, 21] we adjusted for initial stroke severity which may explain the divergence in results. Alternatively, mortality may be insensitive to detecting underlying changes in patient prognosis, and studies focusing on other clinical outcomes, e.g., disability and medical complications, are warranted.

A Taiwanese study showed that higher physician case volume was associated with reduced hospital costs among stroke patients, after adjusting for patient, physician, and hospital characteristics.[14] The study described LOS as a key mediator in this association and further suggested that the favorable volume-cost relationship could be ascribed to more cost-effective and technically effective medical treatment skills and more efficient coordination of the various treatment elements and discharge planning in relation to high case volume.[5, 14]

Figure 1 cautiously suggested that the scale advantages were most evident in stroke units treating up to 300-400 patients annually. This finding is compatible with economic studies which suggest that the scale effect diminishes or is even reverse (diseconomies of scale) in large-scale institutions.[4-6, 38]

It is well-known that stroke care differs between countries,[39, 40] and it is therefore necessary to evaluate whether any distinguishing factors could somehow modify the observed associations before generalizing the findings to other care settings.

In conclusion, we showed that higher stroke unit volume was associated with improved quality of early stroke care and reduced hospital bed-day use. We observed no association between volume and 30-day or one-year mortality.

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FIGURE LEGEND

Figure 1: Volume, quality of care, and outcome (spline curves)

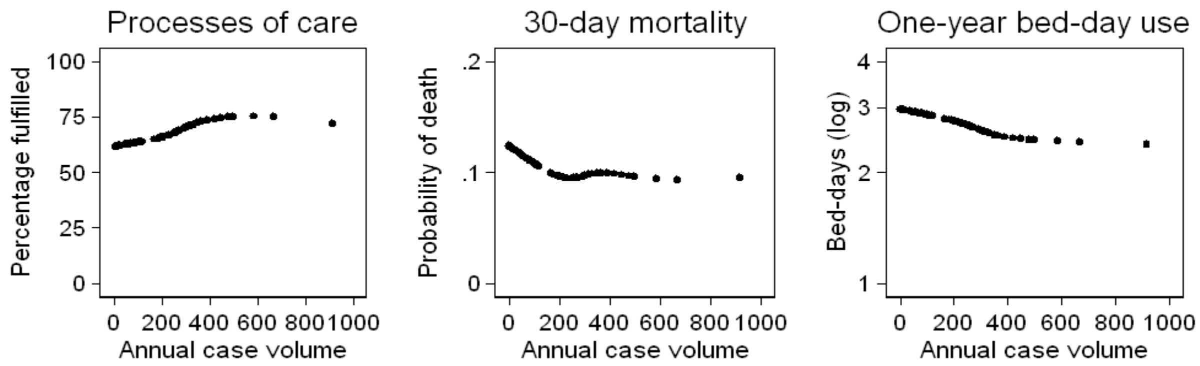

Table 1. Processes of early stroke care

Process of care	**Definition**	**Time limit (days after admission)**
Stroke unit	Admission to a department/unit that is exclusively or primarily dedicated to patients with stroke and characterized by multidisciplinary teams, staff with specific interest in stroke, involvement of relatives, and continuous education of the staff	2
Antiplatelet therapy or anticoagulant therapy	Continuous use of the drug and not merely a single dose	2 or 14
CT/MRI-scan		1
Physiotherapy and occupational therapy	Formal bed-side assessment of the patient´s need for rehabilitation	2
Nutritional assessment	Assessment according to the Gugging Swallowing Screen	2

Table 2. Volume and processes of early stroke care

Process of care (time limit)	Eligible patients n	Process received %	Unadjusted OR (95% CI)
Stroke unit (by day 2)			
Volume 0-231	14,613	86.8	1
Volume 232-330	16,782	90.7	1.48 (0.76-2.90)
Volume 331-498	16,460	93.2	2.08 (1.05-4.15)
Volume 499-915	16,130	95.8	3.44 (1.69-7.00)
Antiplatelet therapy (by day 2)			
Volume 0-231	9,311	78.7	1
Volume 232-330	10,864	83.2	1.34 (0.96-1.87)
Volume 331-498	10,945	87.0	1.82 (1.24-2.66)
Volume 499-915	10,230	84.2	1.45 (0.66-3.21)
Anticoagulant therapy (by day 14)			
Volume 0-231	1,439	65.1	1
Volume 232-330	1,451	66.2	1.05 (0.68-1.62)
Volume 331-498	1,103	73.0	1.45 (0.88-2.41)
Volume 499-915	1,251	53.6	0.62 (0.35-1.09)
CT/MRI scan (by day 1)			
Volume 0-231	14,145	48.2	1
Volume 232-330	16,412	56.4	1.39 (1.00-1.92)
Volume 331-498	16,265	61.6	1.72 (0.99-2.99)
Volume 499-915	15,456	60.6	1.66 (1.02-2.70)

Physiotherapy (by day 2)			
Volume 0-231	12,743	61.2	1
Volume 232-330	14,491	61.3	1.00 (0.72-1.40)
Volume 331-498	13,227	66.8	1.27 (0.78-2.07)
Volume 499-915	12,078	70.8	1.53 (0.87-2.72)
Occupational therapy (by day 2)			
Volume 0-231	12,661	57.0	1
Volume 232-330	14,437	56.7	0.99 (0.73-1.34)
Volume 331-498	13,260	63.3	1.30 (0.83-2.05)
Volume 499-915	12,546	65.4	1.42 (1.11-1.84)
Nutritional assessment (by day 2)			
Volume 0-231	10,819	54.6	1
Volume 232-330	12,728	57.2	1.11 (0.74-1.67)
Volume 331-498	13,691	67.5	1.72 (1.06-2.80)
Volume 499-915	11,168	70.4	1.98 (1.14-3.44)

Table 3. Volume and outcome

	Study population, n	Events, % / Median (IQR)*	Unadjusted ratio (95% CI)*	Adjusted model 1*†	Adjusted model 2*†	Adjusted model 3*†
30-day mortality						
Volume 0-231	14,617	9.6	1	1	1	1
Volume 232-330	16,784	10.0	1.04 (0.85-1.28)	1.10 (0.88-1.37)	1.09 (0.88-1.36)	1.06 (0.86-1.32)
Volume 331-498	16,461	9.9	1.04 (0.84-1.28)	1.13 (0.92-1.37)	1.12 (0.91-1.38)	1.06 (0.88-1.29)
Volume 499-915	16,133	9.4	0.98 (0.82-1.17)	1.10 (0.91-1.32)	1.10 (0.91-1.33)	1.03 (0.87-1.23)
1-year mortality						
Volume 0-231	14,617	21.9	1	1	1	1
Volume 232-330	16,784	21.9	1.00 (0.87-1.15)	1.06 (0.95-1.19)	1.07 (0.94-1.21)	1.07 (0.94-1.22)
Volume 331-498	16,461	21.1	0.96 (0.81-1.13)	1.05 (0.91-1.20)	1.05 (0.92-1.21)	1.06 (0.92-1.21)
Volume 499-915	16,133	19.9	0.89 (0.77-1.02)	1.02 (0.88-1.18)	1.03 (0.86-1.22)	1.03 (0.86-1.24)
Length of stay						

Volume 0-231	14,617	12 (5-27)	1	1	1	1
Volume 232-330	16,784	7 (4-16)	0.67 (0.50-0.89)	0.69 (0.54-0.89)	0.67 (0.55-0.82)	0.70 (0.59-0.83)
Volume 331-498	16,461	6 (3-13)	0.55 (0.43-0.71)	0.60 (0.48-0.73)	0.57 (0.45-0.72)	0.62 (0.50-0.77)
Volume 499-915	16,133	5 (3-9)	0.46 (0.32-0.65)	0.52 (0.38-0.73)	0.49 (0.41-0.59)	0.54 (0.46-0.63)
Bed-days/year						
Volume 0-231	14,617	18 (8-40)	1	1	1	1
Volume 232-330	16,784	15 (6-37)	0.83 (0.69-1.00)	0.88 (0.74-1.03)	0.89 (0.75-1.05)	0.92 (0.78-1.09)
Volume 331-498	16,461	12 (4-34)	0.70 (0.61-0.82)	0.78 (0.69-0.87)	0.78 (0.69-0.89)	0.84 (0.74-0.94)
Volume 499-915	16,133	11 (4-33)	0.68 (0.59-0.78)	0.79 (0.71-0.88)	0.79 (0.70-0.87)	0.85 (0.75-0.97)

[*] Percentage and odds ratio if mortality, and median (interquartile range) and ratio between geometric means otherwise.

[†] Adjusted for age, gender, marital status, housing, alcohol intake, smoking habits, Charlson comorbidity score, atrial fibrillation, hypertension, Scandinavian Stroke Scale score by admission, stroke subtype, treatment with thrombolysis, and calendar year. Model 2 was further adjusted for stroke unit setting and hospital university status, and model 3 was further adjusted for the percentage score for quality of care.

ONLINE SUPPLEMENT
Supplemental table

S1. Descriptive characteristics of 63,995 patients with stroke

Characteristic	Volume 0-231	Volume 232-330	Volume 331-498	Volume 499-915
Age, mean (SD)	72.8 (12.6)	71.9 (13.4)	71.1 (13.6)	70.4 (13.2)
Gender, n (%)				
Male	7,478 (51.2)	8,740 (52.1)	8,682 (52.7)	8,600 (53.3)
Female	7,139 (48.8)	8,044 (47.9)	7,779 (47.3)	7,533 (46.7)
Marital status, n (%)				
Living with someone	7,180 (49.1)	8,499 (50.6)	8,524 (51.8)	8,910 (55.2)
Living alone	6,617 (45.3)	7,118 (42.4)	6,746 (41.0)	6,095 (37.8)
Other form of marital status	341 (2.3)	417 (2.5)	624 (3.8)	337 (2.1)
Missing data	479 (3.3)	750 (4.5)	567 (3.4)	791 (4.9)
Housing, n (%)				
Own home	12,688 (86.8)	14,381 (85.7)	14,052 (85.4)	13,482 (83.6)
Nursing home/institution	969 (6.6)	1,096 (6.5)	1,190 (7.2)	1,020 (6.3)
Other form of housing	275 (1.9)	312 (1.9)	363 (2.2)	501 (3.1)
Missing data	685 (4.7)	995 (5.9)	856 (5.2)	1,130 (7.0)
Drinks/week, n (%)				
> 14 for women and > 21 for men	899 (6.2)	1,057 (6.3)	1,254 (7.6)	1,317 (8.2)
≤ 14 for women and ≤ 21 for men	11,030 (75.5)	12,777 (76.1)	12,356 (75.1)	12,870 (79.8)
Missing data	2,688 (18.4)	2,950 (17.6)	2,851 (17.3)	1,946 (12.1)
Smoking habits, n (%)				
Never	4,144 (28.4)	4,864 (29.0)	4,376 (26.6)	4,890 (30.3)
Daily	4,664 (31.9)	5,193 (30.9)	5,301 (32.2)	5,317 (33.0)
Occasionally	184 (1.3)	235 (1.4)	224 (1.4)	223 (1.4)
Former (> ½ year)	2,888 (19.8)	3,035 (18.1)	3,198 (19.4)	3,323 (20.6)
Missing data	2,737 (18.7)	3,457 (20.6)	3,362 (20.4)	2,380 (14.8)
Atrial fibrillation, n (%)				
Yes	2,585 (17.7)	2,745 (16.4)	2,632 (16.0)	2,298 (14.2)
No	11,348 (77.6)	13,085 (78.0)	13,092 (79.5)	12,548 (77.8)
Missing data	684 (4.7)	954 (5.7)	737 (4.5)	1,287 (8.0)
Hypertension, n (%)				
Yes	7,397 (50.6)	7,915 (47.2)	8,138 (49.4)	6,916 (42.9)
No	6,286 (43.0)	7,635 (45.5)	7,402 (45.0)	7,830 (48.5)
Missing data	934 (6.4)	1,234 (7.4)	921 (5.6)	1,387 (8.6)
Charlson comorbidity score, n (%)				
No comorbidity, 0	5,088 (34.8)	5,374 (32.0)	5,413 (32.9)	5,009 (31.1)
Moderate comorbidity, 1-2	6,638 (45.5)	7,958 (47.4)	7,613 (46.3)	7,763 (48.1)
Severe comorbidity, 3+	2,891 (19.8)	3,452 (20.6)	3,435 (20.9)	3,361 (20.8)
Scandinavian Stroke Scale, n (%)				
Mild (45-58)	6,712 (45.9)	8,864 (52.8)	8,506 (51.7)	8,592 (53.3)
Moderate (30-44)	2,648 (18.1)	3,106 (18.5)	2,732 (16.6)	2,389 (14.8)
Severe (15-29)	1,406 (9.6)	1,636 (9.8)	1,479 (9.0)	1,286 (8.0)
Very severe (0-14)	1,370 (9.4)	1,593 (9.5)	1,486 (9.0)	1,408 (8.7)
Missing data	2,481 (17.0)	1,585 (9.4)	2,258 (13.7)	2,458 (15.2)
Type of stroke, n (%)				
Ischemic	10,268 (70.3)	12,890 (76.8)	12,420 (75.5)	10,361 (64.2)
Intracerebral hemorrhage	1,510 (10.3)	1,669 (9.9)	1,856 (11.3)	1,628 (10.1)
Unspecified	2,839 (19.4)	2,225 (13.3)	2,185 (13.3)	4,144 (25.7)

Thrombolysis, n (%)				
Yes	135 (0.9)	200 (1.2)	666 (4.1)	300 (1.9)
No	14,482 (99.1)	16,584 (98.8)	15,795 (96.0)	15,833 (98.1)
Year of admission, n (%)				
2003	2,292 (15.7)	1,798 (10.7)	1,266 (7.7)	1,780 (11.0)
2004	2,529 (17.3)	2,711 (16.2)	2,141 (13.0)	1,986 (12.3)
2005	2,271 (15.5)	2,844 (16.9)	2,285 (13.9)	2,033 (12.6)
2006	2,006 (13.7)	2,602 (15.5)	2,619 (15.9)	2,813 (17.4)
2007	1,896 (13.0)	2,506 (14.9)	2,493 (15.1)	2,465 (15.3)
2008	1,807 (12.4)	2,166 (12.9)	2,824 (17.2)	2,326 (14.4)
2009	1,816 (12.4)	2,157 (12.9)	2,833 (17.2)	2,730 (17.0)
Stroke unit setting, n (%)				
Neurologic department	1,840 (12.6)	13,129 (78.2)	12,572 (76.4)	12,569 (77.9)
Non-neurologic department	12,777 (87.4)	3,655 (21.8)	3,889 (23.6)	3,564 (22.1)
University hospital, n (%)				
Yes	3,176 (21.7)	6,146 (36.6)	6,524 (39.6)	6,955 (43.1)
No	11,441 (78.3)	10,638 (63.4)	9,937 (60.4)	9,178 (56.9)

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