Medical complications in patients with stroke: Data validity, processes of care, and clinical outcome

PhD thesis

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PREFACE

This Ph.D. thesis is based on studies carried out during my employment at the Department of Clinical Epidemiology, University of Aarhus, and at the DNIP secretariat in The Danish National Indicator Project, Aarhus, during the period 2007–2010.

I would like to express my sincere gratitude to all who made this work possible.
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Århus, May 2010

Den signede dag med fryd vi ser
af havet til os opkomme,
den lyse på himlen mer og mer
os alle til lyst og fromme!
det kendes på os som lysets børn,
at natten hun er nu omme!

N. F. S. Grundtvig, 1826

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LIST OF ABBREVIATIONS

BMI	Body mass index
CI	Confidence interval
CT	Computed tomography
CCI	Charlson comorbidity index score
DNIP	The Danish National Indicator Project
DVT	Deep venous thrombosis
HR	Hazard ratio
H:S	Hovedstadens Sygehusfællesskab
ICD	International classification of diseases
LOS	Length of stay
LPR	Landspatientregisteret
MRI	Magnetic resonance imaging
MRR	Mortality rate ratio
NIP	Det Nationale Indikatorprojekt
NPV	Negative predictive value
NR	Not reported
NRP	Danish National Registry of Patients
OR	Odds ratio
PPV	Positive predictive value
PE	Pulmonary embolism
RCT	Randomized controlled trial
SSS	Scandinavian Stroke Scale
TIA	Transient ischemic attack
UTI	Urinary tract infection
VTE	Venous thromboembolism
WHO	World Health Organization

This Ph.D. thesis is based on the following studies:

I. Ingeman A, Andersen G, Hundborg HH, Johnsen SP. Medical complications in patients with stroke: data validity in a stroke registry and a hospital discharge registry. J Clin Epidemiol 2010;2:5-13.

II. Ingeman A, Andersen G, Hundborg HH, Svendsen ML, Johnsen SP. Processes of care and medical complications in patients with stroke. Submitted.

III. Ingeman A, Andersen G, Hundborg HH, Svendsen ML, Johnsen SP. Medical complications in patients with stroke and clinical outcome: length of stay and mortality. In preparation.

CONTENS

INTRODUCTION

Introduction to stroke

What is stroke?

Stroke is a clinical syndrome with several pathologies.[1] Hippocrates (460 to 370 BCE), known as the father of medicine, was the first to describe the phenomenon of sudden paralysis that is often associated with ischemia. In his writings, Hippocrates used the word “*Apoplexy*”, from the Greek word meaning "struck down with violence”. The word “*stroke*” was used as a synonym for apoplectic seizure as early as 1599 and is a fairly literal translation of the Greek term. In 1658, in his “*Apoplexia*”, Johann Jacob Wepfer (1620–1695) identified the cause of haemorrhagic stroke when he suggested that people, who had died of apoplexy, had bleeding in their brains. Wepfer also identified the main arteries supplying the brain, the vertebral and carotid arteries, and identified the cause of ischemic stroke when he suggested that apoplexy might be caused by a blockage of those vessels.[2-4]

The World Health Organization (WHO) has defined stroke as a clinically defined syndrome “characterized by rapidly developing clinical symptoms and/or signs of focal, and at times global, loss of cerebral function, with symptoms lasting more than 24 hours leading to death with no apparent cause other than that of vascular origin”.[5] Stroke is, however, a heterogeneous disease entity that includes several pathologically different conditions.[6] It can be due to ischemia (lack of glucose and oxygen supply)[7]caused by thrombosis or embolism or haemorrhage. As a result of either, the affected area of the brain cannot function, which may result in a wide variety of symptoms, including an inability to move one or more limbs on one side of the body, to understand or formulate speech, or to see one side of the visual field.[8] Based on medical history, clinical examination and diagnostic tests, including brain imaging, a subclassification of stroke is possible.

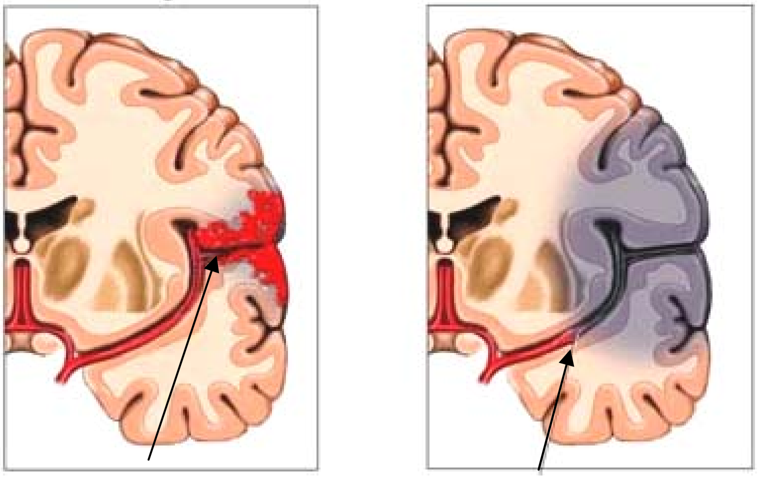


Figure 1: *Drawing of the stroke types.*

Risk factors for stroke

Many factors have consistently been shown to be associated with an increased risk of stroke, and given the burden of stroke, prevention is a major public health concern.[9] The association of these factors with stroke is supported by a large body of experimental and epidemiological scientific work. Risk factors for stroke may be classified as modifiable and nonmodifiable. Fortunately, the list of modifiable risk factors is longer than the list of nonmodifiable factors, which include advanced age, male gender, ethnicity, and hereditary syndromes. Modifiable risk factors for stroke include hypertension, diabetes mellitus, dyslipidemia, smoking, obesity, alcohol abuse, physical inactivity, and atrial fibrillation, among others.[10-12]

Consequences of stroke

A stroke is a medical emergency and can cause permanent neurological damage, complications, and death.[8] It is of major importance for public health internationally because stroke is the second most common cause of death in the Western[8] world, causes approximately 10% of all deaths worldwide, and is a major cause of disability worldwide.[13,14] The 30-day case-fatality among patients with stroke has dropped in recent decades but remains overall between 10-20% in most Western populations.[15]

Those who survive a first stroke are also at risk of a recurrent stroke. The 1-year recurrence rates have been found to vary between 5% and 13% in European, American, and Australian populations[16-18] and five-year recurrence rates range between 16%[17] and 29%[18]. A Danish study reported that 23% of patients admitted to a stroke unit had had a previous stroke.[19] The risk of a recurrent cerebrovascular event is highest in the first month (4%) and at one year (12%) after a stroke, probably reflecting the presence of an active, unstable atherosclerotic plaque.[20] Thereafter, the risk of a recurrent cerebrovascular event falls to about 5% per year, similar to the risk of a coronary event. Predictors of recurrent stroke include increasing age, previous transient ischemic attack (TIA), atrial fibrillation, high alcohol consumption, haemorrhagic index stroke, and hypertension at discharge.[21]

Stroke is also the most frequent cause of serious functional impairment in the adult population. About one half of survivors are left with permanent disabilities and have significant needs for rehabilitation and long-term care.[22]

Stroke often requires prolonged hospitalization and rehabilitation, and a large proportion of patients with stroke and their relatives experience severely reduced quality of life. Besides direct physical consequences such as hemi paresis and aphasia, stroke is also associated with mental and emotional consequences such as dementia, depression, epilepsy, and with secondary medical complications like infections and pressure ulcers.[23]

Further, stroke poses a significant economic burden to society[24], consuming 2% to 4% of the total healthcare cost in developed countries.[25,26]

In Denmark, stroke is the third most common cause of death. About 11% of patients hospitalized with acute stroke and registered in the Danish national stroke database in 2009 died within the first 30 days[27] and 30-40% die within one year after symptom onset.[28] Furthermore another 3,000 experience a recurrent stroke.[28]

During a lifetime one of seven Danes experiences a stroke, and there are an estimated 12,000-14,000 new cases of stroke in Denmark each year. As such, stroke is the disease that results in occupation of most beds in hospitals: approximately 10% of the beds in the large medical sector are used for patients suffering from stroke. The direct cost of treating and caring for people with stroke in Denmark was estimated in 2001 to be 2.7 billion kroner a year. This amount includes both the cost of healthcare and of social care/services. The cost of stroke is equivalent to 4% of total healthcare expenditure. Apart from large costs for home- and hospital-based rehabilitation and care, there are also indirect costs of lost work days and informal care.[28]

The prevalence of stroke is expected to increase greatly during the next 20 years, especially in developing countries, because of the ageing population and decreasing stroke mortality.[29,30] Projections for the European region suggest that the proportion of the population that is age 65 years or older, the group in which most stroke events occur, will increase from 20% in 2000 to 35% in 2050.[31]

Background and existing literature

This section presents the background for the three studies that make up this thesis, including definitions and an overview of the existing literature.

Literature search

The aim of the literature search has primarily been to identify scientific publications that cover the following topics;

- In-hospital complications in patients with stroke during hospitalization with a focus on incidence rates, risk factors, and consequences.
- Validity of registry data on medical complications among patients with stroke.
- The association between quality of care (process) and outcome (medical complications) for patients hospitalized with stroke.
- The impact of medical complications on outcome in terms of length of stay (LOS) and mortality in patients hospitalized with stroke.

The literature search was conducted in international databases. The systematic search was initially conducted in "*PubMed"*, and followed by searches in "*The Cochrane Database*" and *"Google Scholar".*

The search strategy was based on a combination of free-text and MESH-terms search: "Cerebrovascular Accident", "Cerebrovascular Disorders (MESH)", and "Stroke (MESH)", in combination with "pneumonia", "urinary tract infection", "deep venous thrombosis", "pulmonary embolism", "venous thrombosis", "pressure ulcer", "falls after stroke", "constipation", "medical complications", and "complications".

For Study I the keywords were used in combination with "Validation", "data quality", "stroke registry", "predictive value", "data validity"," validity", and "diagnosis".

For studies II and III the keywords were used in combination with "quality of care", "quality assessment", "quality of healthcare", "outcome of care", "process of care", "process assessment", "measuring quality of care", "clinical pathways", "care pathways", "critical pathways", "clinical indicators", "process indicators", "outcome", "length of stay", "mortality", and "case-fatality".

The search was limited to include articles published in English, Danish, Norwegian, or Swedish and involving people age 18 or over. Additional studies were found by searching the reference lists from the identified publications. Additional information from books, reports, and other sources not indexed were also included. The literature and information search was completed in April 2010.

Introduction to medical complications

In medicine, a complication (from the Latin *complicare* meaning 'to fold together'[32]) is an additional problem that arises following a procedure, treatment, or illness and that is secondary to it. Complications are usually directly or indirectly related to a procedure (risk of the procedure), treatment (side effect or toxicity), or illness.[33]

In addition to the initial neuronal damage causing cognitive, functional, and sensory deficits associated with stroke, patients with acute stroke are at high risk of developing a wide range of medical complications.[34,35] Prevention, early recognition, and management of post-stroke complications are regarded as essential aspects of stroke unit care, as many medical complications are potentially preventable or treatable,[36] challenging us to find interventions that can reduce the number and severity of medical complications experienced after stroke.

Although a seemingly number of medical and neurological complications can occur after stroke, this thesis will focus on six (seven where one complication is considered as its two separate manifestations) of the most clinically relevant medical complications: pneumonia, urinary tract infection (UTI), pressure ulcer, falls, venous thromboembolism (VTE, to include deep venous thrombosis (DVT) and pulmonary embolism (PE)), and severe constipation.

Incidence of medical complications

Many studies have examined the complications that occur after stroke, reporting that up to 96% of all patients hospitalized with stroke experience one or more medical or neurological complications during their hospitalization.[35-50]

The most common medical complications are UTI, pneumonia, falls after stroke, pressure ulcer, and constipation, and fewer patients appear to experience symptomatic VTE in modern stroke care. Table 1 gives an overview of the cumulative in-hospital risk of the selected medical complications from 17 studies that have examined multiple complications in patients with stroke. Table 2 presents an overview of studies that focused only on one or two of the seven selected medical complications.

Time of onset

Most medical complications develop within the first few weeks of stroke.[36,38,42,43] A recent Norwegian study found that most complications occurred as early as within the first 24 hours and rarely after 4 days,[35] for example pneumonia, was often apparent early after stroke onset whereas other complications, such as pressure ulcer, VTE, and falls could develop after several days. Many complications are preventable or, when prevention is not possible, amenable to early recognition and treatment to avoid serious consequences from the complications.[51]

Risk factors for complications

Pre-existing medical conditions, advanced age, and pre-stroke disability can affect an individual's risk for developing medical complications. Patients with severe, disabling strokes are particularly vulnerable.[36,38,42-44,49,52] Kalra et al found for example that complications appear to be more common in patients with severe stroke (94%) compared to patients with mild or moderate deficits (16%).[44] Furthermore, fever, hyperglycaemia, systemic inflammatory response, hypoxia, or medications used to treat some of these complications might have a directly damaging physiological effect on an injured brain or might compromise the brain's capability for plastic change.[51]

Table 1. Studies of multiple complications in patients with stroke: cumulative in-hospital risk of selected medical complications.

Complication/ Author, year, country	Sample size, design and setting	Pneumonia %	UTI %	Pressure ulcer %	Falls %	VTE (DVT+ PE) %	Constipation %	Any complication* Rate total %
Sorbello et al 2009[50] Australia	**N = 71, RCT (IS + HS) Multicentre**	*15.5*	*19.7*	*4.2*	*34.0*	DVT: 0.0 PE: 0.0	NR	81.6
Hong et al 2008[41] Korea	**N = 1,254 Prospective (IS) Acute, multicentre**	12.0	*6.9*	*3.3*	*2.2*	NR	NR	24.2
Indredavik et al 2008[35] Norway	**N = 489, prospective (IS + HS) Acute/sub acute Single center**	11.2	16.0	0.6	8.4	DVT: 0.6 PE: 0.6	NR	63.8
Mclean R 2007[47] Singapore	**N = 261, prospective (IS + HS) Acute/sub acute Single center**	NR	65.8	10.8	NR	DVT: 4.2 PE: NR	NR	46.0
Rocco et al 2007[48] Italy	**N = 261, prospective (IS + HS) Sub acute Single center**	10.7[†]	16.2	NR	NR	NR	NR	60.2
Kuptniratsaikul et al 2005[45] Thailand	**N = 327, prospective (IS) Acute, multicenter**	1.2	10.7	2.8	NR	DVT:0.3	NR	71.0
Bae et al 2005[37] Korea	**N = 579, prospective (IS), acute Single center**	10.7#	8.3	1.4	NR	NR	NR	27.6
Hung et al 2005[42] Taiwan	**N = 346 Retrospective (IS + HS) Sub acute Single center**	4.9	13.6	1.5	NR	NR	NR	44.0
McLean D.E. 2004[46] Canada	**N = 133, prospective (IS + HS), sub acute, single center**	2.0	15.0	1.5	20.0	DVT: NR PE: 0.3	NR	67.0
Doshi et al 2003[39] Singapore	**N = 140 Retrospective (IS + HS), sub acute**	5.0	14.3	0.7	4.3	DVT: 0.7 PE: 0.0	22.9	54.3

Complication/ Author, year, country	Sample size, design and setting	Pneumonia %	UTI %	Pressure ulcer %	Falls %	VTE (DVT+ PE) %	Constipation %	Any complication* Rate total %
	Single center							
Weimar et al 2002[52] Germany	**N = 3,866 Prospective (IS) Acute Multicenter**	7.4	6.3	NR	NR	DVT: 0.2 PE: 0.2	NR	29.2
Roth et al 2001[49] US	**N = 1,029 Prospective (IS + HS), sub acute Single center**	4.0	30.5	4.3	10.5	DVT: 4.1 PE: 1.1	NR	75.0
Langhorne et al 2000[36] Scotland	**N = 311, prospective (IS + HS) Acute/sub acute Multicenter**	22.0#	23.0	21.0	25.0	DVT: 2.0 PE: 1.0	NR	85.0
Johnston et al 1998[43] US	**N = 279 Prospective, (IS) Acute/sub acute RCT/multicenter**	10.0	11.0	NR	NR	DVT: 2.0 PE: 1.0	16.0	95.0
Davenport et al 1996[38] Scotland	**N = 607 Retrospective (IS + HS) Sub acute Single center**	12.0 #	16.0	18.0	22.0	DVT: 3.0 PE: 2.0	NR	59.0
Kalra et al 1995[44] UK	**N = 245, prospective (IS + HS) Sub acute Single center**	11.8#	24.5	3.3	NR	DVT: 4.9 PE: 0.8	NR	60.0
Drommerick and Reding 1994[40] US	**N = 100, prospective (IS + HS) Sub acute Single center**	7.0#	44.0	25.0	NR	DVT: 4.0 PE: 0.0	NR	96.0

NR = not reported HS = Haemorrhagic stroke IS = Ischemic stroke RCT = randomized controlled trial

**Any medical or neurological also other complication than the seven mentioned*

† *Pulmonary infection*

Chest infection

Table 2. Studies of one or two complications in patients with stroke: cumulative in-hospital risk of selected medical complications.

Complication / Author, year, country	Sample size, design	Setting	Type of complication	Incidence %	Any complication* Rate total %
Stott 2009[53] **UK**	**N = 412** **Prospective**	IS, acute, Single center	UTI	15.8	NR
Kong et al 2009[54] **Singapore**	**N = 341** **Prospective**	IS + HS, sub acute Single center	VTE	DVT: 9[¤] PE: 0.0	NR
Czernuszenko et Czlonkowska 2009[55] **Poland**	**N = 1,155** **Prospective**	IS + HS, sub acute Single center	Falls	16.3	NR
SU et al 2009[56] **China**	**N = 154** **Prospective**	IS + HS, sub acute Single center	Constipation	55.2	NR
Vermeij et al 2009[57] **The Netherlands**	**N = 521** **Prospective**	IS, acute/sub acute Multicenter	Pneumonia UTI	7.5 4.4	15.0
Ersoz et al 2007[58] **Turkey**	**N = 110** **Prospective**	IS + HS sub acute, chronic Single center	UTI: Symptomatic Bacteriuria	 27.0 39.1	NR
Kwan et al 2007[59] **UK**	**N = 439** **Prospective**	IS + TIA (9%) , acute Single center	Pneumonia UTI	10.0 7.0	NR
Bracci et al 2007[60] **Italy**	**N = 90** **Prospective**	IS + HS, sub acute Single center	Constipation	30.0	NR
Sellars et al 2007[61] **(UK) Scotland**	**N = 412** **Prospective**	IS + HS, acute Multicenter	Pneumonia	19.0	NR
De Silva et al 2006[62] **Singapore**	**N = 111** **Prospective**	IS, acute Single center	DVT: Doppler ultrasound scans - at 7-10 days - at 25-30 days	 30.0 45.0	NR
Ovbiagele et al 2006[63] **US**	**N = 663** **Prospective**	IS , acute Multicenter	Pneumonia UTI	10.0 13.0	NR
Olsson et al 2005[64] **Sweden**	**N = 158** **Prospective**	IS + HS, sub acute Single center	Falls	25.0	NR

Complication / Author, year, country	Sample size, design	Setting	Type of complication	Incidence %	Any complication* Rate total %
Zorowitz et al 2005[65] **US**	**N = 1,161** **Prospective**	IS + HS Multicenter	DVT PE	5.6 NR	NR
Kelly et al 2004[66] **UK**	**N = 102** **Prospective**	IS, acute Single center	Using scan: DVT all DVT proximal PE Clinical: DVT PE	 40.0 17.7 11.8 3.0 5.0	NR
Heutchmann et al 2004[67] **German**	**N = 13,440** **Prospective** **Registry based**	IS, acute Multicenter	Pneumonia PE	6.0 0.4	11.4
Aslanyan et al 2004[68] **Glasgow, UK**	**N = 1,455** **Prospective, RCT**	IS, acute Multicenter	Pneumonia UTI	13.6[#] 17.2	NR
Harari et al 2004[69] **UK**	**N = 146** **Prospective**	IS + HS, sub acute Multicenter	Constipation	66.0	NR
Hamidon et al 2003[70] **Malaysia**	**N = 163** **Prospective**	IS, sub acute Single center	Pneumonia UTI	12.3 3.7	16.0
Teasell et al 2002[71] **Canada**	**N = 238** **Retroprospective**	IS+HS, sub acute Single center	Falls	37.0	NR
Kammersgaard et al 2001[72] **Denmark**	**N = 1,156** **Prospective**	IS + HS, acute/sub acute Multicenter	Pneumonia UTI	7.6 11.4	19.4 (includes 0.4 other infections within 3 days after admission).
Nyberg et Gustafson[73] 1997 **Sweden**	**N = 135** **Prospective**	IS +HS, sub acute Single center	Falls DVT PE	36.0 4.9 0.8	60.0
Nyberg et Gustafson[74] 1995 **Sweden**	**N = 161** **Prospective**	IS, sub acute Single center	Falls	39.0	NR

NR = not reported HS = Haemorrhagic stroke IS = Ischemic stroke RCT = randomized controlled trial
**Any medical or neurological also other complication than the seven mentioned*
† Pulmonary infection
 # Chest infection
¤ used DVT screen protocol with e.g., D-Dimer test

Specific medical complications

Pneumonia

Pneumonia is defined as "inflammation and consolidation of lung tissue due to an infectious agent".[75] Symptoms suggestive of pneumonia are chills, fever, pleuritic chest pain, cough, and purulent sputum.[75]

Post-stroke pneumonia is defined as newly developed pneumonia following stroke onset.[76] Pneumonia is one of the most frequent medical complications of stroke. It has been reported to occur in 1.2% to 22% of patients after acute stroke (Tables 1 and 2). Pneumonia is also the most common cause of fever within the first 48 hours after an acute stroke.[43,77] Most stroke-related pneumonias are believed to result from aspiration.[43] Sellars et al in 2007 found in a prospective cohort of patients with acute stroke that the clinical variables that are most associated with the risk of post-stroke pneumonia are older age (>65 years), speech impairment, severity of post-stroke disability, cognitive impairment, and dysphagia.[61]

Urinary tract infection

In this thesis, UTI is defined as clinical symptoms of urinary infection combined with a positive culture and resistance examination (with significant bacteriuria, $>10^5$/ml). Clinical symptoms suggestive of UTI are supra pubic pains, frequent strangury, malodorous urine, and fever.[78,79] UTI is another of the most common complications of stroke. Previous studies have found highly variable cumulative risks ranging from 3.7% to 65.8% (Tables1 and 2). Stott el al in 2009 found that the median time to post-stroke UTI after admission was 17 days[53], which is comparable to the 15 days observed by Davenport et al.[38] Factors found to predict UTI include stroke severity,[35,80] depressed consciousness level, increased post-void residual urine volume,[80] and diabetes mellitus[53]. The majority of hospital-acquired UTIs are associated with the use of indwelling catheters,[53,81] but whether catheterized or not, patients with stroke have more than double the odds for a UTI when compared with the general medical and surgical populations.[58]

Pressure ulcer

According to the European Pressure Ulcer Advisory Panel a pressure ulcer is defined as "localized injury to the skin and/or underlying tissue usually over a bony prominence, as a result of pressure, or pressure in combination with shear".[82] Immobility-related complications like pressure ulcer vary widely after stroke. Studies have shown that the cumulative risk of pressure ulcers after stroke ranges from 0.6% to 25% (Tables 1 and 2). Known consequences of stroke, like poor mobility and incontinence, increase the risk of skin breaks[51], and it is therefore not surprising that pressure ulcers occur more often in those with more severe strokes.[83] The sacrum, buttocks, and heels are the usual sites for pressure ulcers and should be examined frequently.[51]

Falls

A fall is defined as "an unexpected event in which the participant comes to rest on the ground, floor, or lower level".[84,85]

Patients with stroke are at high risk of experiencing falls, and fall rates have been reported to range from 2.2% to 39% in studies of multiple complications after stroke (Tables 1 and 2).[40,55,64,71,73,74] Studies analyzing falls in stroke patients have been done both in acute stroke units, e.g. Davenport et al and, Langhorne et al,[36,38] and in stroke rehabilitation units, e.g., Mc Lean et al, Roth et al Nyberg et al, and Teasel et al[46,49,71,73,74].

Risk factors for falls in stroke survivors include older age,[38,55] male sex,[73] intercurrent infections,[38,73,86] cognitive impairment, neglect,[55] depression, poly-pharmacy, sensory impairment, and severe stroke-related disability with poor performance in activities of daily living.[55,71,87] Falls are specially common during activities that include transfers, while sitting, and during position changes such as going from a sitting to standing or standing to sitting position. Promoting early mobility after stroke may increase the risk of falls.[55,74]

Falls may be associated with serious injuries including fractures (hip, radial and pelvis); however, the absolute risk of serious injuries following post-stroke falls appears modest (i.e., as low as < 10 %), and in general no higher than in the elderly population without stroke.[88]

Venous thromboembolism

VTE is any thromboembolic event that occurs within the venous system. Then majority of VTE events originate in the calf veins; from there, the thrombosis may progress to the proximal veins, and later, it may break free to lodge in the lungs, where it causes a potentially fatal PE.[89] In this thesis, VTE is defined as "DVT i.e., thrombosis of a deep vein in an extremity (leg or arm), or PE". VTE is a serious complication after acute stroke. Immobility is an important risk factor for VTE, and patients with reduced mobility from a wide variety of causes, including stroke, are particularly susceptible. Most stroke patients have multiple risk factors for VTE, like advanced age, low Barthel Index score, and hemiparesis. Because PE is a major cause of death after acute stroke, the prevention of this complication is crucial.[51,62,66,90]

Deep vein thrombosis

DVT is an important cause of morbidity after stroke and can lead to the sometimes fatal complication of PE.[91]

Tables 1 and 2 show cumulative DVT risks ranging from 0.2% to 5.6%. However, these values are likely to be an underestimate of the incidence of subclinical DVT because patients were not systematically screened with ultrasound or other diagnostic modalities. Thus, the cumulative in-hospital risk of DVT following an acute stroke has been reported to be as high as 40–50% when subclinical DVT events are included.[66,92] The substantial variation in the reported risk estimates for symptomatic DVT shown in Tables 1 and 2 may be the result of the administration of anticoagulants, mobility status, and method of detection used.

Pulmonary embolism

The risk of PE in patients with stroke shows great variation although the risk might have declined in recent years owing to more widespread use of thromboprophylaxis.[90] The reported cumulative risks of symptomatic PE (fatal and non fatal) ranges from 0.2% to 13.0% (Tables 1 and 2). The studies that have focused specifically on VTE complications reported the highest risk estimates of clinically apparent PE (10% to 13%), indicating under identification in studies reporting much lower incidences of PE. Kelly et al in 2004 found that clinical PE occurred overall in 5%. This value changed, however, when they prospectively assessed patients who had received prophylaxis with aspirin and compression stockings, 21 days after stroke onset, using direct thrombus imaging by magnetic resonance with acute ischemic stroke; with these assessments 11.8% had PE.[66]
Most fatal PE occurs between the second and fourth weeks after a stroke.[43] Making a diagnosis can, however, be challenging in individuals who have had a stroke because of accompanying cognitive deficits, speech impairment, or dysphagia. Some stroke survivors who become dysphonic because of aspiration pneumonia, pulmonary infection, or congestive heart failure actually may have associated PE. Often, autopsies after sudden deaths of stroke survivors identify PE as the cause of the death.[91]
One autopsy study reported that PE was the most common cause of death between the second- and fourth-week following stroke which suggests that PEs are often subclinical and/or unrecognized after stroke.[93]

Constipation

There is no widely accepted, clinically useful definition of constipation. However, constipation may, according to the most-used definition, be defined as “evacuation of faeces less than three times a week”, and often involves hard, dry stools that are painful or difficult to pass. One study has demonstrated that diaries may be a valid way to evaluate frequency and/or consistency.[94,95]
Constipation following stroke has not been well studied. Of the 17 studies that looked at multiple complications, only two included constipation as a complication. Yet, constipation is a frequent

complication after stroke with reported cumulative risks ranging from16% to 66%.[39,43] However, some single complication studies (Table 2) have looked specifically at constipation as a complication post-stroke and reported incidences ranging from 30%- 66%.[56,60,69]
Possible risk factors for constipation among stroke patients include old age, use of a number of different drugs, dehydration, poor dietary fibre and physical inactivity.[95] Although a high risk of constipation has been reported, there does not appear to be a direct causal mechanism between stroke *per se* and constipation. As such, constipation is viewed as an avoidable complication of stroke.[95]

Consequences of medical complications

The occurrence of medical complications has been shown to contribute to poor outcome because these complications may hinder optimum rehabilitation, increase the length of hospital stay and resource use[37,42,86,96,97] e.g., the presence of UTI and pneumonia has been associated with an increased LOS of 41% (31% to 51%),and 52% (40% to 65%), repsectively.[98] Furthermore, medical complications have been associated with increased mortality.[35,36,38,43,49,52,67,99]. A recent German study from 2008 estimated that more than 50% of all in-hospital deaths among patients with stroke were caused by serious medical or neurological complications.[67]

Limitations of existing literature

Despite the apparent serious consequences of medical complications the available data on causes of medical complications are sparse and inconclusive[35,36,38,40,49,67,99], and differences in the types of complications considered, diagnostic criteria, and patient populations make it difficult to compare directly the reported risk estimates. The studies also span more than a decade, during which time stroke management has changed considerably. The changes in stroke care might also potentially have changed the risk of medical complications, and findings from existing studies should therefore be treated with caution.

Medical complications and data validity

Introduction: use of hospital discharge and other disease registries in research on medical complications in stroke

The considerable burden of stroke on the patients, their families, and society, and the development of improved diagnostic tools and acute treatment within the last decades have prompted an epidemiological effort to examine treatments and processes of care that might help patients recover more quickly and/or prevent complications, and to study the consequences of medical complications on prognosis.[100] Large-scale population-based studies, reflecting real-life conditions in modern stroke care, are much needed. However, primary data collection is often time-consuming and costly; consequently, it is often only done on a smaller scale. Furthermore, there is a likelihood of bias due to recall, non-response, and effects on the diagnostic process as a result of the research question.[101,102] Clinical and administrative registries are possible alternatives to primary data collection; they have the advantage of providing readily available data and often contain complete registration of information on people in the target population. Registries are generally valuable tools for answering clinical, administrative, and research questions and may also be useful for studying medical complications in patients with stroke; however, a documented, reasonable validity of the data is a prerequisite for using such data sources.

Existing literature

Virtually no data exists on the data quality of medical complications among patients with stroke; However, as Table 3 presents some studies have validated medical complications in different patient populations (e.g., unselected internal medicine patients, pregnant women, patients from geriatric wards, general practice, or with a former cancer diagnosis). These studies found moderate to high positive predictive values (PPVs) of the diagnosis studied.[103-113] The PPVs reported from these studies ranged from 20.7% for pressure ulcer to 96.2% for pneumonia.[103-106,108-113] Only a few studies have examined the sensitivity and specificity of diagnoses of medical complications in registries. Quan et al investigated diagnoses of complications in Canadian administrative hospital discharge data and found that the sensitivity ranged from 0% to 57.1% (higher than 50% for only two conditions). In contrast, specificity was generally high (range: 99.0–100%).[107]

Limitations of existing literature

To our knowledge, information on the validity of registry data on medical complications among patients with stroke has not been reported previously. Nevertheless, data from other patient populations suggest that the PPVs of medical complications are moderate to high and that there is a lack of reported values for the sensitivity and specificity of diagnoses of medical complications in registries.

Table 3. Prior studies on the validity of medical complications diagnoses.

Author, year, country	Sample size and design	Setting and population	Data Source /method used	Type of complication	Results
Severinsen et al 2009[108] Denmark	**N = 1,100 Validation study**	Participants of the Danish cohort study Diet, Cancer and Health, in the period from 1994 to 2006.	The Danish National Patient Registry and Medical records Record review.	VTE	Overall PPV: 75.0% (95% CI: 71.9–77.9) discharged from wards. The PPV varied by type: DVT: 71.3% (95% CI: 67.4–75.0) PE: 82.1% (95% CI: 77.2–86.4)
Zhan et al 2009[113] American	**N = 25,525**	Random samples of Medicare discharges in 2005 to 2006. Hospital discharge abstracts (2005) from the states of New York and California ICD-9-CM codes in Medicare Claims.	Database was the Medicare Patient Safety Monitoring System Medical records Medicare claims.	UTI	PPV: 30% Sensitivity: 65% ICD-9-CM codes in Medicare claims have very limited validity in identifying UTI.
Skull et al 2008[109] Australian	**N = 5,101 Case cohort Validation study**	>65 years Two large tertiary hospitals Randomly selected from all discharges.	ICD10 codes to identify hospital pneumonia cases Medical records Chest x-ray report and both.	Pneumonia	PPV: 96.2 % (95% CI: 95.4–97.0) Sensitivity: 97.8 % (95% CI: 97.1–98.3) Specificity: 96.9 % (95% CI: 96.2–97.5)
Gunningberg et al 2008[104] Sweden	**2002: N = 357 2006: N = 343 Validation study**	Inpatients at departments of surgery, medicine and geriatrics in 2002 and repeated in 2006.	Electronic health records (EHR) and patient records. Audit and physical examination.	Pressure ulcer	The prevalence of pressure ulcers obtained by auditing paper-based patient records 14.3%, compared with 33.3% in physical inspection. Four years later there was after implementation of EHR 20.7 % recorded pressure ulcers and 30% found by physical inspection.
Zhan C et al[112] 2007 American	**N = 20,868 Validation study**	Surgical hospitalizations Random samples of hospital discharges of Medicare beneficiaries in 2002-2004.	Identification of postoperative DVT/PE events was compared using ICD-9-CM codes and medical record abstraction.		232 DVT cases and 95 PE cases were identified by ICD-9-CM codes; 108 DVT cases and 31 PE cases by medical record abstraction. 72 DVT cases and 23 PE cases by both methods.

Author, year, country	Sample size and design	Setting and population	Data Source /method used	Type of complication	Results
					PPV of ICD9-CM coding: DVT: 31% PE: 24% Combined : 29% Sensitivity: DVT: 67% PE: 74% Combined : 68%
Thomsen et al 2006[110] Denmark	**Validation of a N = 100 records from a population-based cohort study**	North Jutland County All adults hospitalized with a first-time diagnosis of pneumonia were identified in hospital discharge registries. A random sample of 10 of the selected hospital records for each of the 10 years of the study period 1994 through 2003.	The Danish National Patient Registry Medical records Record review.	Pneumonia	PPV 90% (95% CI: 82–95%).
Larsen et al 2005[105] Denmark	**N = 300 medical records Validation study**	North Jutland County January 1980. December 2001 Women: during pregnancy and postpartum	Hospital discharge registries Medical records Record review.	VTE: DVT+PE	VTE: Overall PPV of all the selected codes: 87.3% (95% CI: 83.0–90.9). DVT: 86.3 % (95% CI: 83.0–69.9) PE: 81.8 % (95% CI: 59.7–94.8).
Arnason et al 2005[103] Canada	**N = 616 medical records Validation study**	Tertiary care hospital Patients: A random sample of patients discharged September 1999 -September 2000 with an ICD-9-CM code indicating a thromboembolic diagnosis including VTE.	Hospital discharge abstracts Medical records.	Incident and prevalent VTE.	VTE PPV 74% (95% CI: 64.0–82.0).
White et al 2004[111] US, California	**N = 600 pregnancy-specific codes N = 400 standard**	Pregnant women in whom there were one or more pregnancy-specific (600codes) or standard ICD-9-CM. codes	Record review Charts abstracted to determine the presence of objectively documented	VTE	VTE 214 diagnoses PPV: Pregnancy-specific VTE code: 31% (95% CI: 24–38%).

Author, year, country	**Sample size and design**	**Setting and population**	**Data Source /method used**	**Type of complication**	**Results**
	VTE codes **Validation study**	(400 codes) for VTE	VTE.		Standard VTE code: 80% (95% CI: 63–99%).
Quan et al 2004[107] **Canada**	**N = 1,200** **Validation study**	Randomly selected adult inpatient separations Alberta, occurring between April 1, 1996 and March 31, 1997	Administrative hospital discharge register The corresponding medical charts.	To evaluate the accuracy of complications	Specificity range: 99.0–100% Sensitivity ranged from 0% to 57.1% Cerebrovacular disease : 57.1 %, UTI : 55.6% Pneumonia: 35 % Constipation: 9.5 % (No 95% CI reported) PPV Cerebrovacular disease : 100 %, UTI : 62.5% Pneumonia: 50.0 % Constipation: 40.0 % (No 95% CI reported).
Lawrenson et al 2000[106] **UK**	**N = 1,384** Controls =1,384 Cases = 285 Case cohort **Validation study**	Women who had a diagnosis of first event of DVT or PE, had evidence of treatment with an anticoagulant and had a record of a prescription for a combined oral contraceptive.	The UK General Practice Research Database Hospital discharge summaries Death certificates.	E(DVT+PE)	Information was available for 177 VTE events 84 supported by hospital investigation or Death certificates.

Quality of treatment and care and medical complications in patients with acute stroke

Introduction to quality of care

Monitoring the quality of stroke care has become an important issue in recent years. The number of countries that have developed clinical guidelines for acute stroke care has increased rapidly over the past decade. Clinical guidelines, or 'gold standards' are being developed to facilitate the translation of best evidence into practice, and to standardize stroke care. Clinical guidelines focus on the recommended processes of care. These have been largely medically oriented, primarily because of the available scientific evidence. However, with growing interest in the possible benefits of nonmedical interventions including commencing rehabilitation early after stroke,[114-116] recent updates to the guidelines have involved the inclusion of guidelines for early rehabilitation, particularly mobilization. In Denmark, the first set of national guidelines was published in 1994, and they have since been updated in 2005 and 2009. These guidelines recommend early initiation of treatment, care and rehabilitation, which is in line with international guidelines including the "Helsingborg Declaration 2006 on European Stroke Strategies", and "The European Stroke Initiative Recommendations for Stroke Management 2008".[34,117,118]

Process and outcome measures in patients with stroke

The quality of care provision can be divided into structures of care, processes of care, and outcomes.[119] *Structures of care* refer to characteristics of the healthcare system such as organization, staff, and use of technologies. Structures of care are generally governed by a regional healthcare organization or by individual hospitals and are dependent on available resources. *Processes of care* refer to how patient care strategies are applied, including initial evaluation at admission, early admission to a stroke unit, early initiation of rehabilitation and secondary prevention. *Outcomes* refer to the patient's response to treatment, such as functional gains and quality of life. These three components interact so that the proper structure allows for optimal processes of care, which in turn affect outcomes. Figure 2 shows examples of processes of stroke care.

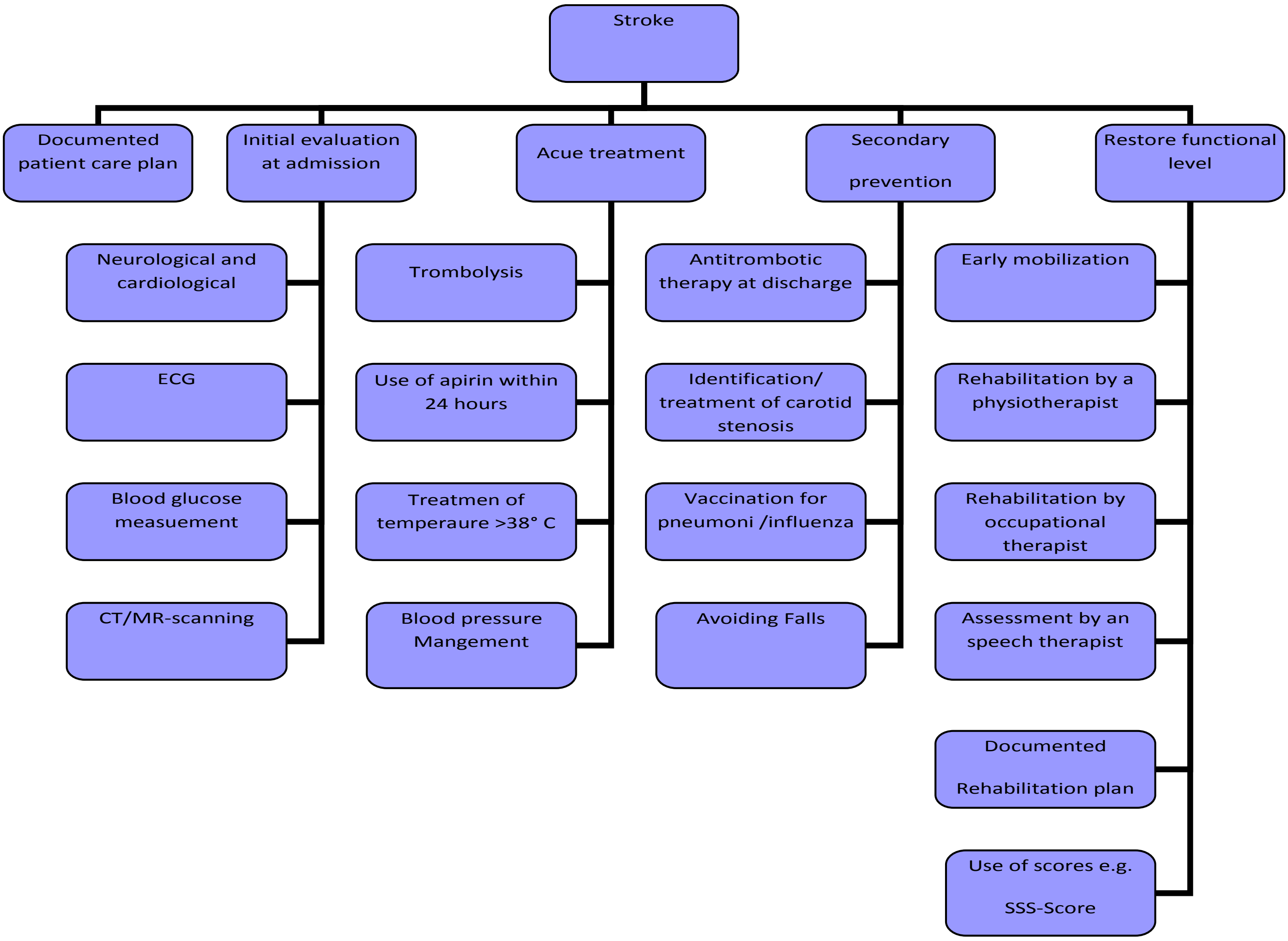


Figure 2. Examples of processes of stroke care.

Assessing quality of care requires the development and application of processes of care. Processes of care are explicit evidence-based standards of care used to monitor and evaluate quality of clinical care.[120] It is desirable that the indicators selected to measure quality of care reflect clinical guideline recommendations and the evidence base. Generally, process indicators are more sensitive and more responsive to changes in clinical care and often are collected over a shorter time period.[121] Because quality of care reflects both processes and outcomes, assessment of quality may also include outcome measures. These measures include mortality, length of stay (LOS), and complication rates.[122] As Figure 3 shows; stroke has a wide range of possible outcome measures. Outcome measures require standardized data collection, large sample sizes, and stringent case mix adjustment to ensure differences are not associated with inherent variations in the patient population.[121]

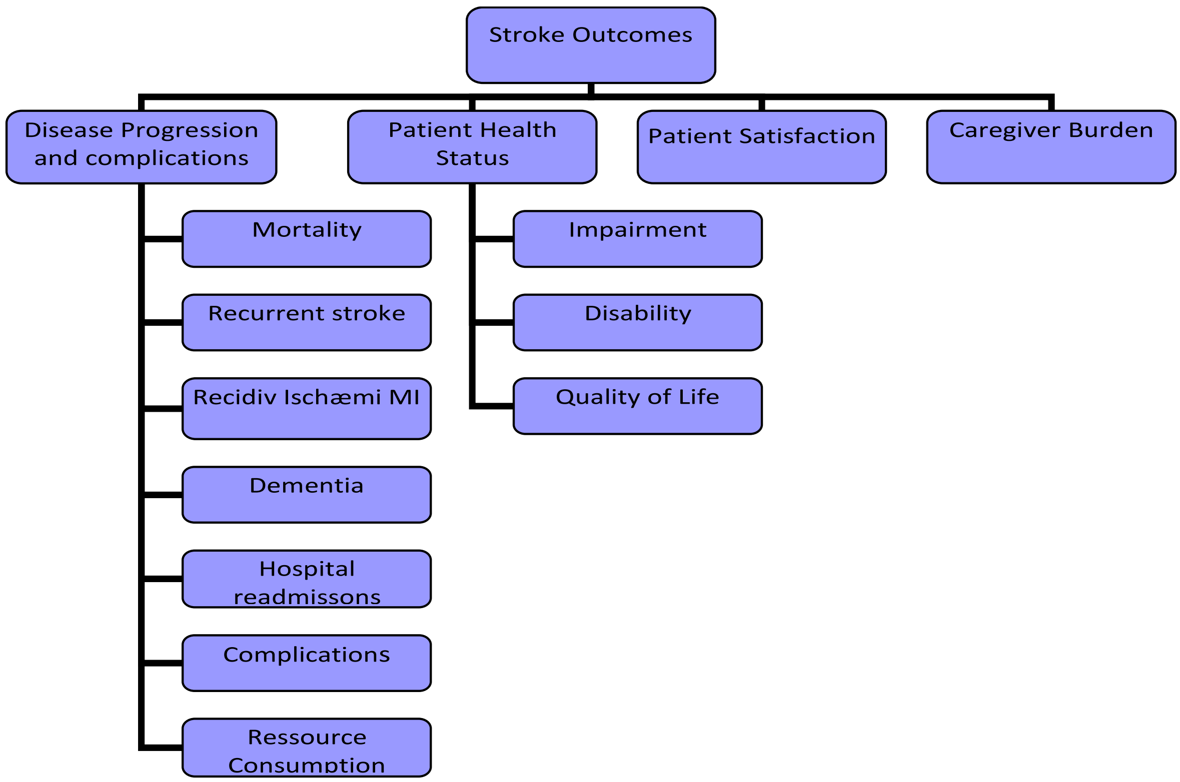


Figure 3. Examples of outcome measure for patients with acute stroke.[120]

Both structures and processes of care, however, need to be optimized to establish an ideal stroke care system. Structures of care alone do not result in better patient outcomes, but improved structures allow processes of care to function optimally, and processes of care (or the adherence to best evidence/best practices) improve outcomes. Processes of care differ within systems of care because of factors that include resource availability, financial incentives, accountabilities, and cultural traditions.[123]

In this thesis, process measures will be referred to as processes of care.

Table 4. Processes of care and medical complications in patients with stroke.

Author, year, country	Sample size and design	Intervention/ quality of care criteria	Study population	Outcome of interest	Results
Rotter et al 2010[124]	**N = 11,398** **27 studies** **Cochrane Review**	Twenty studies compared stand alone clinical pathways with usual care. Seven studies compared clinical pathways as part of a multifaceted intervention with usual care.	Different study populations: e.g. , hip and knee arthroplasty , and stroke.	Professional practice, patient outcomes: e.g. complications, wound infections, bleeding and pneumonia LOS Hospital costs	The 20 studies indicated a reduction in in-hospital complications OR 0.58 (95% CI: 0.36–0.94). In the seven studies no evidence of differences were found between intervention and control groups.
Cuesy et al 2010[125] **Mexico**	**N = 223** **RCT** **Multicenter**	Group A: Standard treatment + early mobilization in the form of passive turning and mobilization Group B: Standard treatment.	IS admitted to two university hospitals Medical unit and emergency unit.	Pneumonia	Decrease in pneumonia in group A RR 0.39 (95% CI:0.39–0.79)
Sorbello et al 2009[50] **Australia**	**N = 71** **Secondary analysis from RCT** **Multicentre**	Early mobilization Two group randomly assigned to receive standard care (SC) or SC plus very early mobilization (VEM) until discharge or 14 days.	IS + HS Required to react to verbal commands Temperature < 38.5°C. Two stroke units.	Complications including death	No significant group differences in the number, type or severity of complications by 3 month after stroke
Czernuszenko et Czlonkowska 2009[55] **Poland**	**N = 1,155** **Prospective** **Sub acute** **Single center**	Rehabilitation	IS + HS Neurological rehabilitation unit.	Falls	The risk of falls increased with increasing efficiency of rehabilitation > 1.313 Barthel points/week: unadjusted HR 3.6 (95% CI: 2.1- 6.0).

Author, year, country	Sample size and design	Intervention/ quality of care criteria	Study population	Outcome of interest	Results
Kwan et al 2004[126] **UK**	**N = 4,421** **Three RCT: N = 340** **12 nonrandomized studies: N = 4,081** **Cochrane review**	Evaluated the effects of care pathways, as compared to standard medical care.	Among patients with acute stroke admitted to hospital.	Dead Dependent Complication rates Process of care Readmission rates Patient and carer satisfaction Quality of life LOS Hospitalization costs.	UTI: Six non-randomized studies (n = 1283): Significantly fewer UTI in the care pathway group OR 0.51 (95% CI: 0.34–0.79) Pneumonia: Four non-randomized studies (n=797) No significant difference OR 0.89 (95% CI: 0.53–1.5).
Perry et al 2003[127] **UK**	**N = 400** **Prospective quasi-experimental design**	Evidence-based guidelines for nutrition, including early assessment of nutritual risk and early assessment of a physiotherapist or an occupational therapist.	IS + HS admitted to 11 medical and elderly care wards with possible later transfer to a stroke unit.	Compliance with guidelines Changes in weight BMI Barthel index score LOS Discharge destination, Time (days) to starting nutritional support Death/survival Complications.	Significant reduced risk of post stroke pneumonia and UTIs. At baseline 33 patients had pneumonia. Post implementation 13 patients Incidence of urinary tract infection 26 episodes compared to 11.

HS= Haemorrhagic stroke, IS = Ischemic stroke, RCT = randomized controlled trial, BMI = Body mass index

Existing literature: processes of care and medical complications

It is widely accepted that stroke unit care results in better outcome with fewer deaths and lower disability[128], and this knowledge has led to important changes in stroke service delivery around the world. Randomized clinical trials (RCTs) have also demonstrated the efficacy of some specific processes of care in relation to stroke outcomes, in addition to admission to specialized stroke units; these processes include use of thrombolysis, antiplatelet drugs, and oral anticoagulants for selected patient groups.[126,128,129] Further, a number of observational studies have linked higher quality of care, as indicated by compliance with clinical guidelines, with improved patient outcomes including lower LOS, lower risk of death, and less disability among patients with stroke.[130-134] A positive association has been reported for overall guideline compliance in most studies,[130,133,135] and some studies have also reported positive associations for specific processes of care i.e., initiation of antiplatelet therapy, swallowing assessment, and assessment by a physiotherapist.[131,132]

However, only a few studies have examined an association between processes of care and medical complications in patients with stroke. Studies of medical complications following stroke are generally difficult to perform, because they require a systematic approach, as well as valid reporting in a sufficiently large population.[38,40,43,44,49,128] Table 4 shows the existing relevant studies on processes of care and medical complications.

Perry et al, in their 2003 prospective study of 400 patients with acute stroke, demonstrated that implementation of evidence-based guidelines for nutrition in acute stroke, including early assessment of nutritional risk and early assessment by a physiotherapist or an occupational therapist, of acute stroke was associated with a reduced risk of post-stroke pneumonia and UTIs.[127]
In the most recent Cochrane systematic review (Kwan 2004), which included three randomized and 12 nonrandomized studies, patient management with stroke care pathways (a plan of care that is developed and used by a multidisciplinary team, and is applicable to more than one aspect of care), was found to be associated with a lower risk of developing certain complications, including UTIs and readmissions. No significant differences in risk were found for other complications such as pneumonia, pressure ulcer, falls, DVT, and constipation, although the point estimates indicated that patient management with stroke care pathways might have a protective effect.[126]
Czernuszenko et al, in a 2009 prospective study of 1,155 patients with stroke, identified an increased risk of falling with increased efficiency of rehabilitation.[55]
In a recent RCT, Cuesy et al demonstrated that early mobilization in the form of passive turning and mobilization applied in patients during the acute phase of an ischemic stroke decreased the incidence of pneumonia.[125]

Bernhardt et al in a recent RCT 2008 (n=71) showed that commencing mobilization early after stroke was not harmful, but there also was no effect on differences in death and dependency at three months between those who undertook an early intensive mobilization protocol and those who did not.[114] This result was confirmed by Sorbello et al in 2009, who found no significant group differences in the number, type, or severity of complications at 3 months after stroke between the group that received standard care vs. the group receiving standard care plus very early mobilization.[50]

Finally, a recent Cochrane Review (in 2010) by Rotter et al concluded that clinical pathways (guidelines) applied on different study populations (e.g., hip and knee arthroplasty, stroke) were associated with reduced in-hospital complications. Complications assessed included wound infections, bleeding and pneumonia.[124]

Overall, the evidence supports the use of care pathways in acute stroke care[136] and an early multidisciplinary effort to ensure optimal care to prevent medical complications. The presence of medical complications, such as pneumonia, UTI, and VTE, is generally regarded as a negative indicator of quality of care.[137,138]

Limitations of existing literature

In reality little is known about the association between processes of care as reflected by fulfillment of specific processes of care criteria for a range of specific processes and the risk of medical complications in patients with acute stroke. The existing studies are in general characterized by relatively small sample sizes, and most patients were not treated in stroke units. Furthermore, the majority of studies to date have examined the effects of adherence to different sets of guidelines rather than the effect of specific processes of care. This distinction makes it difficult both to interpret existing studies and to apply their findings directly to clinical practice. Finally, the validity of the data registered on medical complications is uncertain in previous studies. In conclusion, the effectiveness of specific processes of care in preventing medical complications remains uncertain.

Medical complications and outcome

The following section presents the relevant studies on the association between medical complications and LOS and mortality. It should be remembered that a broad range of factors (related to patients, physicians, and the healthcare system) interact to explain clinical outcomes for patients with acute stroke. Figure 4 shows factors that influence stroke outcome.[139]

The illness: Stroke
Type of stroke: ischemic /haemorrhagic
Severity
Location
Size

\+

The patient
Age
Sex
Ethnicity
Genetic factors
Comorbidity e.g. cardiac disease
Diabetes, hypertension
Medical treatment
Lifestyle: smoking habits, alcohol intake

\+

Diagnosis
Access to healthcare
Timing of hospitalization
Initial evaluation at admission
Timing of CT/MRI-scan

\+

Treatment (acute, secondary prevention)
Restore functional level
Timing of treatment
Trombolysis
Anti thrombotic treatment (IS)
Early mobilization
Early rehabilitation
Blood pressure management

\+

Clinician performance
Competence/experience
Motivation
University vs. local hospital
Stroke unit/general ward
Resuscitation orders
Rehabilitation programs
Compliance to guidelines/processes of care

\+

Patient compliance
Medical therapy
Rehabilitation plan /physical activity
Prevention of recurrent stroke

=

Clinical outcome
Mortality
Disability
Complications
Readmissions
Quality of life

Figure 4. Factors that influence stroke outcome. Modified from Sackett.[139]

Length of stay and medical complications in patients with acute stroke

Introduction

LOS has been identified as the main cost-determining factor for patients with acute stroke, and given the current pressure to reduce the cost of medical care, an essential approach is to shorten LOS. One approach that has proven to reduce LOS is implementation of clinical guidelines in stroke units.[134,140]

A number of previous studies have examined the causes of increased LOS in patients with stroke. Medical causes include the severity of stroke, greater comorbidity, surviving until discharge, and nonmedical causes that include living in an institution and marital status.[141-144]

In this thesis, LOS was defined as the time span from hospital admission to hospital discharge.

Table 5. Medical complications and LOS.

Complication / Author, year and, country	Sample size, Design, and setting	All patients LOS Mean/ median days	Unadjusted LOS Mean/ median days *with* complication	Unadjusted LOS Mean/ median days *without* complication	Adjusted LOS
Tong et al 2010[145] **US**	**N = 1, 150** **Retrospective** **(IS), sub acute** **Multicenter** **Registry study**	NR	Mean: – with UTI : 8.3 – with pneumonia: 13.4 – with DVT : 12.7 – with PE: 13.7	Mean: – without UTI: 4.4 – without pneumonia: 4.5 – without DVT: 4.7 – without PE: 4.7	NR
SU et al 2009[56] **China** **Constipation**	**N = 154** **Prospective** **(IS + HS), sub acute** **Single center**	Median: 22.0 (15.0, 29.0)	Median – with constipation: 24.0 (18.5, 32.5)	Median – without constipation: 17.0 (13.0, 27.0)	The patients that stayed longer than 2 weeks had higher rate of constipation than those stayed less than 2 weeks (63.0% versus 28.6%) p<0.001.
Kong et al 2009[54] **Singapore** **VTE**	**N = 341** **Prospective** **(IS + HS)** **Acute/sub acute** **Single center**	Mean: Acute unit: 23.4 Rehabilitation unit: 30.6	NR	*NR*	*NR*
Vermeij et al 2009[57] **The Netherlands** **Infections**	**N = 521** **Prospective** **(IS) , acute/sub acute, multicenter**	Median: 10.0 (6.0, 21.0)	Median – with infection: 18.5 (10.5, 33.0)	*NR*	*NR*
Czernuszenko et al 2009[55] **Poland** **Falls**	**N = 1,155** **Prospective** **(IS + HS), sub acute** **Single center**	Mean: 28.9	Mean: – Fall : 34.0	Mean: – No fall: 27.9	Probability of experiencing a first fall increases with LOS.
Sorbello et al 2009[50] **Australia** **Early mobilization**	**N = 71, RCT** **(IS + HS)** **Multicenter**	Median : – Standard Care: – 7.0 (3.0–26.0) – Very early – mobilization: – 6.0 (3.0–51.0)	*NR*	NR	OR 1.18, 95 CI: 1.06–1.32, p = 0.002 associated with experiencing an immobility-related complications (falls, pneumonia , DVT, PE, pressure ulcer, UTI,) i.e. for every extra day of hospital stay, holding all other variables constant, the number of complications is expected to increase by 5.3%.

Complication / Author, year and, country	Sample size, Design, and setting	All patients LOS Mean/ median days	Unadjusted LOS Mean/ median days *with* complication	Unadjusted LOS Mean/ median days *without* complication	Adjusted LOS
Kwan et al 2007[59] UK Pneumonia UTI	**N = 439 Prospective (IS + TIA (9%)) Acute Single center**	NR	Median – with infection: 14.0 (5–23)	Median – without infection: 7.0 (3–14.3)	P< 0.001
Indredavik et al 2008[35] Norway 35	**N = 489 Prospective (IS + HS) Acute/subacute Single center**	Mean: 12.0	*NR*	*NR*	*NR*
Rocco et al 2007[48] Italy	**N = 261 Prospective (IS + HS) Sub acute Single center**	Mean: 14.8	NR	*NR*	*NR*
Ovbiagele et al 2006[63] US Infections	**N = 663 Prospective (IS), acute Multicenter**	NR	Median: – with UTI: 7 .0 – with pneumonia: 4.0	Median: – without UTI: 4.0 – without pneumonia: 13.0	Adjusted Cox proportional hazards <u>Reference group: with complication</u> – UTI: Relative hazard: 0.54 – Pneumonia: Relative adjusted: 0.26.
Bae et al 2005[37] Korea	**N = 579 Prospective (IS) Acute Single center**	NR	Complication YES % * – < 7 days 16.9 – 7-13 days 15.7 – 14-29 days 30.7 – <= 30 days 36.7	Complication NO%* – < 7 days 22.3 – 7-13 days 50.8 – 14-29 days 20.6 – <= 30 days 6.3	NR
Kuptniratsaikul et al 2005[45] Thailand	**N = 327 Prospective (IS + HS) Subacute Multicenter**	NR	NR	NR	Patients with a prolonged hospital stay (>21 days) had a greater risk of complications 2.36 (95% CI: 1.26–4.43).
Hung et al 2005[42] Taiwan	**N = 346 Retrospective (IS + HS) Subacute Single center**	Mean: 28.0	Mean: – with complication: 33.9	Mean: – without complication: 18.6	p <0.0001

Complication / Author, year and, country	Sample size, Design, and setting	All patients LOS Mean/ median days	Unadjusted LOS Mean/ median days *with* complication	Unadjusted LOS Mean/ median days *without* complication	Adjusted LOS
Saxena et al 2007[97] **Singapore**	**N = 200** **Prospective** **(IS and HS)** **Sub acute** **Multicenter**	Mean: 34.0 Median: 32.0 (min 3.0 max 136.0)	Mean: – with complication: 36.6 Median: – with complication: 34.0	Mean: – without complication: 27.0 Median: – without complication: 24.0 p <0.01.	Multiple linear regression analysis of length of stay the significant independent factors positively associated with LOS were medical complications occurring in rehabilitation.
Spratt et al 2003[146] **Australia** **In-hospital infection: presence of either pneumonia or UTI**	**N = 257** **Prospective** **(IS + HS), acute** **Single center**	Mean: 21.0 Median: 9.0 (6.0, 23.0)	NR .	NR	In-hospital infection were associated with prolonged hospital stay: OR 3.6 (95% CI: 1.7–7.7).
Hamidon et al 2003[70] **Maylasia** **Infections**	**N = 163** **Prospective** **(IS), acute** **Single center**	Mean: 7.48	NR	NR	NR
Weimar et al 2002[52] **Germany**	**N = 3,866** **Prospective** **(IS)** **Acute/sub acute** **Multicenter**	Mean: 14.7 Median:13 (9,18)	Median: – with complication:13.0 (7;23)	Median: – without complication:12.0 (9;17)	NR
Roth et al 2001[49] **US**	**N = 1,029** **Prospective** **(IS + HS)** **Subacute** **Single center**	Mean: 28.0 +/- 13.8	NR	NR	NR
Kammersgaard et al 2001[72] **Denmark** **Infections**	**N = 1,156** **Prospective** **(IS + HS)** **Acute /subacute** **Multicenter**	NR	Mean: – with complication: 57.0	Mean: – without complication: 32.7	In multiple linear regression analysis, early infection delayed discharge from hospital by mean 9.3 days.
Tirschwell et al 1999[98] **US** **Pneumonia** **UTI**	**N = 4,757** **Prospective** **(IS)** **Population based**	Mean: 7.8	Mean: – with complication mean: 10.0	Mean: – without complication: 7.1 p <0.0005	Multiple linear regression: – Pneumonia: 51.7% (95 CI: 39.6–64.8) increase in LOS.

Complication / Author, year and, country	Sample size, Design, and setting	All patients LOS Mean/ median days	Unadjusted LOS Mean/ median days *with* complication	Unadjusted LOS Mean/ median days *without* complication	Adjusted LOS
	hospital discharge database **Multicenter**				– UTI: 41% (95 CI: 30.9–51.4) increase in LOS.
Davenport et al 1996[38] **Scotland**	**N = 607** **Retrospective** **(IS + HS)** **Subacute** **Single center**	Mean: 37	Increased likelihood of experiencing a complication with an increased LOS. Length of stay >30 days: OR 12.9 (95% CI: 7.7–22.0)	NR	NR
Karla et al 1995[44] **UK**	**N = 245** **Prospective** **(IS + HS)** **Subacute** **Single center**	NR	NR	Frequency of complication and LOS Beta 0.28, p less than 0.01.	
Drommerick and Reding 1994[40] **US**	**N = 100** **Prospective** **(IS + HS)** **Subacute** **Single center**	Mean: 52	NR	NR	Number of complications per patient varies with the length of stay.

NR = not reported HS = Haemorrhagic stroke IS = Ischemic stroke RCT = randomized controlled trial

Existing literature: medical complications and LOS in patients with acute stroke

The majority of studies on medical complications have reported a mean or median LOS of (1) the overall population and/or (2) with and without complications, e.g., pneumonia and UTI. Mainly the mean LOS or median LOS is given as a part of the descriptive tables of the study population. In addition, the mean LOS ranges from 7–52 days depending on the setting of the studies, e.g., unselected groups of patients among those hospitalized for stroke rehabilitation or those hospitalized for acute ischemic stroke (Table 5). Overall the studies in Table 5 indicate that occurrence of medical complications is associated with longer LOS.

Dromerick and Reding in 1994 completed one of the early studies on medical complications (n=100) and showed in a single-centre cohort study that the number of complications per patient varied with LOS, although it was not possible to determine if the prolonged hospitalization was a cause or effect of stroke-related complications. The older patients may have been waiting for nursing home placement which would prolong the hospital stay.[40] This idea was confirmed by the Scottish prospective cohort study (n=609) of Davenport et al in 1996.[38] They reported an increased likelihood of experiencing a complication with an increased LOS. In line with Drommerick et al, they suggested, this result might reflect that these patients were under observation longer, rather than either the possibility that those with severe strokes had more complications or that complications prolonged the hospital stay.[38] Similar to this report, a 2005 Thai cohort study of 327 in-rehabilitation patients reported that patients with a prolonged hospital stay (>21 days) had a greater risk of complications (2.36; (95% confidence interval (95% CI): 1.26–4.43).[45] Further, both Kalra et al in 1995 and Hung et al in 2005 reported, in line with Davenport et al, that the occurrence of complications was significantly associated with patients who required longer rehabilitation.What remains unclear in these studies is whether this association was because of a longer stay that resulted in the patient's experiencing more complications or because the occurrence of complications had prevented or delayed participation in rehabilitation and lengthened LOS.[42,44]

A cohort study by Saxena et al in 2007 (n= 200) at two hospitals in Singapore found that the characteristics most clearly associated with LOS were medical complications.[97] In line with this study the results from Tirschwell et all 1999 showed that the presence of UTI or pneumonia was associated with an increased LOS of 41% (31% to 51%), and 52% (40% to 65%), respectively.[98] Pneumonia and UTI are the most frequently studied complications with a huge impact on LOS.[57,59,63,98,145,146] For example, a 2006 California study addressed pneumonia and UTI and their influence on outcomes during hospitalization among 663 patients with ischemic stroke in the California Acute Stroke Prototype Registry patients admitted to 11 hospitals. The authors found that both pneumonia and UTI were associated with significantly greater LOS with a relatively adjusted increase of LOS of 74% and 46% respectively.[63]

Information is sparse on pressure ulcer, falls, VTE, and constipation and their impact on LOS. Yet, in a 2009 prospective cohort study (n=1,155) of risk factors for falling during inpatient rehabilitation Czernuszenko et al found that the probability of experiencing a first fall increases with LOS. In the univariate analysis of LOS comparing patients who fell and patients who did not fall there was a significant difference in mean LOS values, which were 34 and 27.9 days, respectively.[55] Similarly, a Chinese prospective cohort study from 2009 (n =154) found that patients with constipation stayed longer in the hospital than those without constipation (median LOS 24 and 17 days, respectively).[56]

Finally, Sorbello et al in 2009 reported that longer LOS was significantly associated with experiencing a higher number of complications and complications related to immobility, (odds ratio (OR): 1.18, 95% CI: 1.06–1.32). In addition, they found that higher LOS was associated with experiencing immobility-related complications (pneumonia, UTI, pressure ulcer, falls, DVT, and PE); i.e., for every extra day of hospital stay, holding all other variables constant, the number of complications is expected to increase by 5.3%.[50]

In contrast to other studies, a 2002 German study by Weimar et al involving 3,866 patients with ischemic stroke found only a minor difference in median LOS values between patients with complications (median LOS: 13.0 (7, 23) days) and without complications (median LOS: 12.0 (9, 17) days).[52]

In conclusion, previous studies indicate that medical complications have a huge impact on LOS in particular with regard to infections, which the majority of studies examined. Limited data exist regarding the impact of other severe medical complications on LOS, like pressure ulcer, falls, DVT PE, and constipation.

Table 6. Medical complications and mortality.

Complication / Author, year and country	Sample size, design, and setting	Setting	Type of complication	Period of mortality reported	Unadjusted mortality estimates %	Adjusted mortality estimates
Nedeltchev et al 2010[147] Switzerland	**N = 479 Prospective**	**IS Acute/sub acute Single center**	Any complication	30 day-mortality	Overall: 13.0 Cause of dead: pneumonia: 19.0	NR
Tong et al 2010[145] Atlanta US	**N = 1,150 336 Retrospective**	**IS, sub acute Multicenter Registry**	Any complication	In-hospital mortality	NR	All 5 complications except UTI in 2006 to 2007 were independent predictors of n the multivariable analysis in both time periods with PN, PE, and AMI being the strongest predictors of in-hospital mortality.
Stott DJ[53] Scotland 2009 UTI	**N = 412 Prospective**	**IS + HS Acute/sub acute Single center**	UTI	3 months	UTI: 15.8	UTI associated with death or disability at 3 months, but not significantly.
Vermeij et al 2009[57] The Netherlands	**N = 521 Prospective**	**IS Acute /sub acute Multicenter**	Pneumonia UTI	1- year mortality	With stroke-associated infection: 47.0	Stroke-associated infection: – Adjusted HR 1.5 (95% CI: 1.0–2.4) Pneumonia: – Adjusted HR 2.1 (95 %CI: 1.2–3.7) –
Sorbello et al 2009[50] Australia	**N = 71 RCT**	**IS + HS Multi-centre**	Early mobilization	3 month mortality	Overall mortality: 15.5	
Hong et al 2008[41] Korea	**N = 1,254 Prospective**	**IS Acute Multicentre**	Any complication	Within the 3-month:	Overall: 7.3 Causes of deaths: Pneumonia: 14.3 recurrent stroke: 5.5	NR
Indredavik et al 2008[35] Norway	**N = 3,631 Prospective**	**IS Acute/sub acute Multi center**	Any complication	3 month mortality	Overall: 17.2	NR

Complication / Author, year and country	Sample size, design, and setting	Setting	Type of complication	Period of mortality reported	Unadjusted mortality estimates %	Adjusted mortality estimates
Saposnik et al[148] 2008 Canada	**N = 489 Prospective**	**IS + HS Acute/sub acute Single center**	Pneumonia PE	30- day case-fatality 1- year mortality	Overall: 12.6 Overall: 23.6 Unadjusted OR: Pneumonia: – 30 day: OR 3.27 (95% CI: 2.86-4.70) – 1 year: OR 5.70 (95% CI: 3.91-7.48) PE: – 30 days: OR 1.57 (95% CI: 01.47-5.23) – 1 year: OR 2.30 (95% CI: 1.01-4.86)	In-hospital pneumonia was associated with 30-day and 1-year case fatality. Pneumonia: – 30 days: OR 1.91 (95% CI: 1.23–2.95) – 1 year: OR 2.21 (95% CI: 1.53–3.19) No data for PE because PE was not associated with increased mortality after adjustment.
Kwan et al 2007[59] UK	**N = 439 Prospective**	**IS + TIA (9%) acute Single center**	Pneumonia, UTI	In-hospital mortality	– with infection: 26.0 – without infection: 9.6	Adjusted OR: 2.50 (95% CI: 1.27–4.90)
Rocco et al 2007[48] Italy	**N = 261 Prospective**	**IS +HS Sub acute Single center**	Any complication	In-hospital mortality	9.2	UTI: OR 4.92 (95% CI: 2.19–11.04) associated with a higher risk of mortality
Ovbiagele et al 2006[63] US	**N = 663 Prospective**	**IS Acute Multicenter**	Pneumonia UTI	In-hospital mortality	– with UTI: 8.3 – without UTI: 7.4 Unadjusted OR 1.05 (95% CI: 0.56- 1.96) – with pneumonia: 27.3 – without pneumonia: 5.3 Unadjusted OR 6.38 (95% CI: 3.83- 10.6)	UTI yes compared to no UTI: – Adjusted OR 0.83 (95% CI: 0.43–1.57) Pneumonia yes compared to no pneumonia – Adjusted OR 5.96 (95%C: 3.02–11.7)

Complication / Author, year and country	Sample size, design, and setting	Setting	Type of complication	Period of mortality reported	Unadjusted mortality estimates %	Adjusted mortality estimates
Bae et al 2005[37] **Korea**	**N = 579** **Prospective**	**IS** **Acute** **Single center**	Any complication	30- day mortality 1- year mortality	Mortality higher compared with those without complications. The 30-day mortality: - with complications: 16.3, - without complications: 1.4 1-year mortality: - with complications: 46.9 - without complications: 8.8	One or more medical complications: 30 days : adjusted OR 2.67(95% CI: 1.89–3.78) 1 year: adjusted OR 1.94 (95% CI: 1.14–3.29).
Kimura et al 2005[149] **Japan**	**N = 15,322** **Prospective**	**IS + TIA** **1 year follow-up only completed for 10,981 patients**	Pneumonia	1- year mortality	IS: 7.0 TIA: 3.5	Cause of dead : Pneumonia: 22.6%
Asaylan et al 2004[68] **UK**	**N = 1,455** **Prospective** **RCT**	**IS** **Acute/sub-acute** **Multicenter**	Pneumonia UTI	3 months mortality Patients alive at day 7	Between infectious events at day 7 and poor outcome at 3 months outcome in univariate modelling Pneumonia: Unadjusted HR:5.1 (95% CI: 3.6–7.3) UTI: Unadjusted HR: 1.8 (95% CI: 1.1–2.7).	After correcting for prognostic factors in patients alive at day 7 Pneumonia: Adjusted: HR 2.2 (95% CI: 1.5–3.3) UTI: Adjusted: HR 1.04 (95% CI: 0.67–1.6).
Heuschmann et al 2004[67] **Germany**	**N = 13,440** **Prospective**	**IS + HS** **Acute/sub acute** **Single center**	Any complication	In-hospital mortality	Overall: 4.9. Pneumonia was the complication with the highest attributable proportion of death in the entire stroke population, accounting for 31.2% (95% CI: 30.9–31.5) of all deaths.	NR

Complication / Author, year and country	Sample size, design, and setting	Setting	Type of complication	Period of mortality reported	Unadjusted mortality estimates %	Adjusted mortality estimates
					More than 50% of all in-hospital deaths were caused by serious medical or neurological complications 54.4% (95% CI: 54.3%–54.5%).	
Katzan et al 2003[150] US	**N = 11,286 Prospective**	**IS + HS Acute/sub-acute Multi center**	Pneumonia	30-day mortality	Unadjusted : – with pneumonia: 26.9 – without pneumonia: 4.4	After adjusting for admission severity and propensity for pneumonia, Pneumonia: – RR 2.99 (95% CI: 2.44–3.66). Estimated that 10% of deaths within 30 days of admission among hospitalized patients with stroke are attributable to pneumonia.
Vernino et al 2003[100] US	**N = 444 Retrospective Case-control Medical record review Autopsy data**	**IS Multi center** Follow-up data were available for 100% at 30 days, 99% at 1 year, and 98% at 5 years after IS.	Any complication	1 month mortality 6 month mortality 1-year mortality 5- years mortality	17.0 23.0 29.0 5 years: 54.0 Causes of death at 1 month: Respiratory infection: 21% (e.g., pneumonia). Causes of death at 1 year: Respiratory infection: 26%	NR
Hamidon et al 2003[70] Singapore	**N = 163 Prospective**	**IS Acute Single center**	Pneumonia UTI	In-hospital	Overall: 11.7 (95% CI: 7.2–17.6)	Early infection increased mortality OR 14.83 (95% CI: 4.31–51.1).
Weimar et al 2002[52] Germany	**N = 3,866 Prospective**	**IS Acute Multicenter**	Any complication	In-hospital	Overall: 6.8 - With complication: 16.9 - Without complication: 1.2 From: - pneumonia: 0.6	NR

Complication / Author, year and country	Sample size, design, and setting	Setting	Type of complication	Period of mortality reported	Unadjusted mortality estimates %	Adjusted mortality estimates
					- PE: 0.2 - DVT: 0.0 - UTI: 0.0 - Recurrent stroke: 0.4	
Kammersgaard et al 2001[72] Denmark	**N = 1,156 Prospective**	**IS + HS Sub acute Single center (+ community based)**	Pneumonia UTI	In-hospital	- With complication: 32.0 - Without complication: 17.7	In multiple logistic regression analysis adjusted for covariates, death during hospital stay was not independently predicted by early infection p = 0 .78.
Roth J et al 2001[49] US	**N = 1,029 Prospective**	**IS + HS Sub acute Single center**	Any complication			
Langhorne et al 2000[36] Scotland	**N = 311 Prospective** Patients only included after he fourth day of hospitalization.	**IS + HS Acute/subacute Multicenter**	Any complication	In-hospital 6 months mortality 18 months mortality 30 months mortality	Overall: 19.0 29.0 42.0 50.0	NR
Tirshweel et al 1999[98] US	**N = 4,757 Prospective**	**IS Population-based hospital dicharge database Multicenter**	Any complication >5%	In-hospital mortality		Multivariate logistic regression analysis of the associations of complications with hospital fatality: UTI: Adjusted OR 0.6 (95% CI:0.4-0.8) Pneumonia: Adjusted OR 3.7 (95% CI: 2.8-4.8).
Johnston et al 1998[43] US	**N = 279 Prospective**	**IS + HS Acute/sub acute Multicenter**	Any complication	3 month mortality	14.0 Cause of death: medical complications: 51.0 New stroke: 8.0	NR
Davenport et al 1996[38] Scotland	**N = 607 Retrospective**	**IS+ HS Sub acute Single center**	Any complication	In-hospital mortality	22.4	Complications were associated with an increased risk of death during admission OR 1.9 (95% CI: 1.2–2.9)
Karla et al 1995[44] United Kingdom	**N = 245 Prospective**	**IS + HS Sub acute Single center**	Any complication	In-hospital mortality	General medical ward: 12.0 Stroke unit: 7.0%	

Complication / Author, year and country	Sample size, design, and setting	Setting	Type of complication	Period of mortality reported	Unadjusted mortality estimates %	Adjusted mortality estimates
Bamford et al 1990 [15] **UK**	**N = 675 Prospective**	**IS + HS Acute Multi center**	Immobility related complications: considered pneumonia, PE, and sepsis together.	30-day mortality	675/129 =19.1 Due to immobility rela ted complications: 45/129 35.0	NR
Silver et al 1984[151] **Canada**	**N = 1,073 Prospective**	**IS + HS Acute Single center**	Pneumonia PE	In-hospital mortality 2th- 4th week after admission	IS: Pneumonia 28/79 = 35.4 HS: Pneumonia 2/10 = 20.0 IS: PE 4/79 = 0.05 HS: PE 0/0 = 0	NR

NR = not reported HS = Haemorrhagic stroke IS = Ischemic stroke RCT = randomized controlled trial

Existing literature: medical complications and mortality in patients with acute stroke

Introduction

The European consensus declaration on stroke strategies (Helsingborg Declaration) recommends that all countries aim to evaluate stroke outcome and quality of stroke management.
The recommendation on mortality is that 85% of stroke patients should survive the first month after stroke.[118] There are no recommendations for mortality beyond one month.

A number of previous studies have examined factors associated with mortality after stroke. Among these, the direct neurological sequelae of the stroke are the most common cause of death. The other factors that have most consistently been reported are age and stroke severity. However, diabetes, atrial fibrillation, and cardiovascular event are also strong predictors of death after stroke[21,67,147,148,152-155] A recent Swedish study published in 2008 found also that impaired functional outcome after stroke is an independent predictor of poor survival. The mechanism behind this association could be a higher risk of complications.[36,156]

Existing literature: medical complications and mortality in patients with acute stroke

Most studies have reported on the overall mortality[35,36,41,50,147,149] and /or the in-hospital death [36,38,44,48,52,59,63,67,70,72,151] or 30-day mortality.[15,37,68,100,147,148,150] Yet, some studies have also reported 3-month mortality or 1-year mortality.[35-37,41,43,50,53,57,100,148,149] Table 6 shows the relevant studies addressing medical complications and mortality.
In their 1996 paper, Davenport et al found that medical complications were associated with an increased risk of death during the hospital stay (unadjusted OR: 1.9; (95% CI: 1.2–2.9)) (multivariate statistics were not included in the analyses).[38] In a 1998 study by Johnston et al the authors concluded that medical complications accounted for 50% of deaths three months after stroke.[43] In 2004, Heuschmann et al in a large registry-based study involving 13,440 patients with ischemic stroke confirmed the findings of Davenport et al and Johnston et al.[67] In that study the authors found that more than 50% of all in-hospital deaths were caused by serious medical or neurological complications.[67]
Bae et al in 2005 (n =579) showed in a prospective cohort study of patients with acute ischemic stroke that the 1-year mortality was higher for those with complications compared to those without complications (adjusted OR: 1.94 (95% CI: 1.14–3.29)).[37]
In 1984, Silver et al examined early mortality following stroke in a prospective cohort study (n=1073) and reported that after the first week, during which neurological sequelae of the stroke were the most common cause of death, pneumonia was the major cause of death, accounting for 35.4% for ischemic stroke and 20% for haemorrhagic stroke.[151] A few years later, in 1990, Bamford

et al confirmed this finding reporting that 35.5% of all deaths during the first 30 days resulted from immobility related complications like pneumonia and PE.[15] In subsequent years several studies, in spite of different study designs, different populations and changes in stroke treatment and care, are in accordance with the findings of Silver et al and Bamford et al.[38,43,44,57,59,67,68,70,98,100,148-150] In 2003, Katzan et al reported in a large prospective study (n=11,286) that pneumonia was a leading cause of death in the post-acute phase of stroke, accounting for approximately 30% of the 30-day mortality.[150] This finding was confirmed by another large German registry study involving 13,440 patients with ischemic stroke that reported pneumonia to be the complication with the highest attributable proportion of death in the entire stroke population, accounting for 31% of all in-hospital deaths.[67] In 2009, Vermeij et al estimated the increased risk of mortality at 1-year in patients with post-stroke pneumonia to be doubled.[57,148] All together, the majority of previous studies on mortality and complications/infections have shown that post-stroke pneumonia is a strong predictor of both short- and long-term morality, and suggested that proper management of pneumonia may improve short- and long-term prognosis for patients with acute stroke.
There are, however, more limited and inconsistent data published on the association of UTI with mortality. Some studies have found no significantly increased risk of mortality.[48,53,68,70] and some others have found that UTI was associated with a decreased risk of in-hospital mortality.[63,98]

Some studies have found that VTE is one of the most important contributors of mortality in patients with stroke.[67,93] On the other hand in 2008 Saposnik et al found that PE was not associated with increased mortality after adjustment for prognostic factors.[148]

The evidence of the impact on mortality of pressure ulcer, falls, and constipation after stroke is sparse. As for falls, the primary subject of interest has not been mortality but the incidence of serious injuries like fractures (hip, radial, and pelvis), which often are as low as <10% and in general no higher than in the elderly population without stroke.[88] However, a previous study has indicated that stroke unit care appeared to reduce the risk of death attributable to complications related to immobility.[157]

In summary, these studies indicated that medical complications are associated with an increased risk of death. In particular stroke-associated pneumonia infection is independently associated with mortality after stroke. The studies suggested that taking measures to prevent pneumonia, aggressively managing pneumonia, and reducing the period of immobilization could potentially prevent early stroke-related complications.

Limitations of existing studies on LOS and mortality

The existing studies are limited by methodological problems:

- Some of the studies have relatively small sample sizes, which gives rise to statistically imprecise risk estimates and complicates the interpretation.
- They were carried out in different units (rehabilitation/acute care setting /stroke units/clinical trial setting) and in settings that are not comparable with modern stroke treatment.
- In addition the studies may not be generalizable, because are based on selected patient populations involving e.g., inclusion only of patients with ischemic stroke.
- Studies use different definitions of medical complications and some use retrospective identification of complications from case notes which may be influenced by the diagnostic criteria used, and the standard of note keeping.
- The studies have different lengths of follow-up and varying degrees of adjustment, if any, for potential confounding factors.

In conclusion, results from existing studies should therefore be treated with caution and large-scale population-based studies, reflecting real-life conditions in modern stroke care, are much needed to examine the association between medical complications and LOS and mortality.

AIMS OF THE THESIS

The aims of this thesis were as follows:

1. To examine the validity of data related to medical complications among patients with stroke in two population-based Danish registries: the Danish National Indicator Project (DNIP) and the Danish National Registry of Patients (NRP) *(Study I).*
2. To examine the association between processes of care and the risk of medical complications in patients with acute stroke in a population-based follow-up study (*Study II)*.
3. To examine the association between in-hospital medical complications and LOS and the 30-day and 1-year mortality in patients with acute stroke in a population-based follow-up study *(Study III)*.

MATERIALS AND METHODS

Setting

All three studies were conducted in the former Copenhagen Hospital Corporation and Aarhus County (approximately 1.3 million inhabitants). The population is primarily Caucasian. As in all of Denmark, the entire population in the counties is provided tax-supported health care by the Danish healthcare system allowing free access to hospital care and general practitioners. Patients with acute medical conditions, including stroke, are exclusively admitted to public hospitals. The entire population was covered by a large number of administrative and medical registries, which are used for monitoring and regulating all central aspects of the public sector including the healthcare system.[158]

Study designs

Validity study (study I)

To examine the validity of data related to medical complications, we conducted a validation study among patients with stroke in two population-based Danish registries: the DNIP and the NRP. In Study I we indentified patients with acute stroke who had been admitted and discharged between January 13, 2003 and December 31, 2006. In total, 8,024 admissions in the registry were eligible for inclusion.

Cohort design (studies II and III)

Studies II and III were both follow-up studies examining among patients with acute stroke, admitted to stroke units in the former Copenhagen Hospital Corporation and Aarhus County, and registered in the DNIP. In *Study II* we identified all patients with acute stroke who had been admitted and discharged between January 13, 2003 and December 31, 2008. In total, 11,757 admissions were available for analysis.

In *Study III* we identified all patients with acute stroke who had been admitted and discharged between January 13, 2003 and December 31, 2009. In total, 13,721 admissions were available for analysis.

Table 7 gives an overview of the structure of studies II and III. The classification of the different variables used is described in the section; *Definition of study population, exposure and outcomes.*

Table7. Design of the studies II and III.

Study	Source population	Exposure	Outcomes
II	All admissions for acute stroke, from 10 specialized stroke units in the former Copenhagen Hospital Corporation and Aarhus County, registered in the DNIP.	Processes of care	Medical complication(s): Pneumonia Urinary tract infection Pressure ulcer Falls after stroke Venous thromboembolism Constipation Any complication*
III	All admissions for acute stroke, from 10 specialized stroke units in the former Copenhagen Hospital Corporation and Aarhus County, registered in the DNIP.	Medical complication(s): Pneumonia Urinary tract infection Pressure ulcer Falls after stroke Venous thromboembolism Constipation Any complication*	LOS 30-day and 1-year mortality

* One or more of the six mentioned medical complications

Data sources

Below is a detailed description of the data sources used in this thesis.

The Civil Registration System (studies I+III)

Since 1968 The Civil Registration System has been updated on a daily basis by using a civil registry number unique to each Danish citizen that encodes sex and date of birth, and unambiguous linkages between the population-based registers can be made (Figure 5).

The Central Personal Registry since 1968 has been storing electronic records of all changes in vital status and migration for the entire Danish population, including changes in address, date of emigration, and the exact date of death since 1968. The register also includes, among other variables, marital status, citizenship, kinship, profession and declaration of incapacity.[159,160]

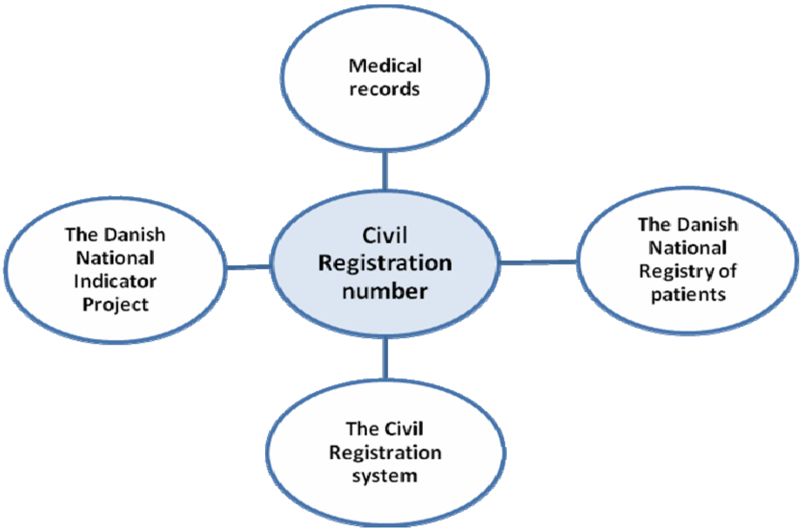


Figure 5. Data sources for studies I - III

The Danish National Indicator Project (DNIP) (studies I-III)

In 2000, the DNIP was established as a nationwide initiative to monitor and improve the quality of treatment and care provided by the Danish healthcare system for specific diseases, including stroke. The project develops evidence-based quality criteria related to the structure, process, and outcome of healthcare and monitors the fulfillment of these criteria. Project participation is mandatory for all Danish hospitals, relevant clinical departments, and units treating patients with stroke. Upon hospital admission, data on care and patient characteristics (e.g., age, sex, marital status, housing, Scandinavian Stroke Scale (SSS) score, history of stroke or myocardial infarction, previous and/or current atrial fibrillation, hypertension, diabetes mellitus, intermittent claudication, smoking habits, and alcohol intake) are collected for all patients admitted with stroke.

The SSS score was used to assess admission stroke severity.[161] This scale is a validated and widely used neurological stroke scale in Scandinavia that evaluates level of consciousness; eye movement; power in the arm, hand, and leg, orientation, aphasia, facial paresis, and gait with a total score that ranges from 0 to 58.[162] The SSS score can be assessed reliably either face-to-face or from routine hospital admission records. We defined four levels of the score: very severe (0–14), severe (15–29), moderate (30–44), and mild (45–58).

Detailed written instructions are available to staff to ensure the validity of the data collected and completeness of patient registration in the DNIP. After hospital discharge, the data are entered into a central database. A structured audit process is carried out regularly (every year) on a national, regional, and local basis to assess critically the quality of the dataset and results. After the audit process is completed, the data are released publicly, including comments on the results from the audit groups. To ensure completeness of patient registration in the DNIP, its enrolees are compared with local hospital discharge registries.[163]

The Danish National Registry of Patients (NRP) (studies I-III)

The NRP is an administrative nationwide public registry that has covered all discharges from somatic hospitals in Denmark since January 1, 1977. The data include the civil registry number, the dates of admission and discharge, the surgical procedure(s) performed, and up to 20 diagnoses for every discharge classified, from 1994, according to the Danish version of the International Classification of Diseases tenth edition (ICD-10). All discharge diagnoses are assigned by the physician who discharges the patient. Each hospital contact is represented by one discharge record describing service dates, which are dates of admission and discharge for inpatients, dates of first and last visit for outpatients, and date of visit for emergency room patients. Reporting of all data concerning each hospital contact is mandatory.[164]

Medical Records

In Study I, medical records from a random sample (5%, n=417) of patients from the 10 stroke units in the former Copenhagen Hospital Corporation and Aarhus County were retrieved and reviewed by a single reviewer (Annette Ingeman) using a standardized form (Appendix I). The form was developed and tested in close collaboration with two consultants in neurology and clinical epidemiology (Grethe Andersen, Søren Paaske Johnsen). The criteria used to define the presence of a complication (Appendix II) were in accordance with existing international defined criteria or, if such criteria were not available, defined a priori by consensus among the authors. Additionally, we retrieved and reviewed 25 medical records for each of the seven types of complications registered in the DNIP. In total, 589 records were retrieved and reviewed.

Definition of study population, exposure and outcomes

The study population

In all three studies we identified all admissions for acute stroke, from the 10 stroke units in the former Copenhagen Hospital Corporation and Aarhus County, registered in the DNIP. All patients (≥18 years) admitted to Danish hospitals with stroke, as defined by WHO criteria, i.e., an acute disturbance of focal or global cerebral function with symptoms lasting more than 24 hours or leading to death of presumed vascular origin, are eligible for inclusion in the DNIP database. This includes patients with intracerebral haemorrhage and ischemic stroke (ICD-10: I63, infarction; I61, haemorrhage; and I64, unspecified). 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 Computed tomography (CT) or Magnetic resonance imaging (MRI) scan are also excluded.

Although some patients had multiple events, we included only the first stroke event registered in the DNIP during the study period. Furthermore, only patients with a valid civil registry number were included in the study.

Medical complications in the NRP (Study I)

Information on medical complications during the hospital admission was obtained through linkage to the NRP. We retrieved data on the following ICD-10 discharge diagnoses: pneumonia (DJ12–DJ18), UTI (DN30.0, DN30.8, DN30.9, and DN10), pressure ulcer (DL899), falls (DR297 and EUHE), DVT (DI82.9, DI82.9A–E), PE (DI26), and constipation (DK590). Both primary diagnoses, (i.e., the condition, the principal reason for the hospital admission), and secondary diagnoses (all other clinically relevant diagnoses), including any significant complications and symptoms that appeared during the admission, were identified from the registry.

Medical complications in the DNIP (studies I–III)

During hospital admission, detailed data on each patient are prospectively registered using a standardized form. The data include the presence or absence of the following seven medical complications: pneumonia, UTI, pressure ulcer, falls, DVT, PE, and constipation. DVT and PE were combined in studies II and III into one category, “VTE”, as there were few events. Only complications that occurred after hospital admission are registered.

In ***Study II*** medical complications was the ***outcome*** whereas in ***Study III*** medical complications was the ***exposure*** (Table7).

Processes of care (studies II and III)

In ***Study II,*** the nine processes of care were the ***exposure*** whereas they were included in ***Study III*** as a ***possible confounding factor*** because they have been linked to post-stroke mortality[131]. We computed a variable containing the percentage of relevant processes of care received for each patient in Study III as a measure for in-hospital stroke care.

An expert panel including physicians, nurses, physiotherapists, and occupational therapists identified nine processes of care covering the acute phase of stroke.[163] A time frame was defined for each to capture the timeliness of the processes (Table 8).

With a standardized registration form with detailed written instructions, data regarding the processes were prospectively collected from the time of admission as part of the daily clinical work of healthcare professionals taking care of the patients. Patients were classified as eligible or noneligible for the specific processes of care depending on whether the stroke team or physician treating the patient identified contraindications; e.g., severe dementia in a patient with ischemic stroke and atrial fibrillation precluding oral anticoagulant therapy or rapid spontaneous recovery of motor symptoms, making early assessment by a physiotherapist and an occupational therapist irrelevant. In the written instructions, the criteria for deeming a patient ineligible for the care processes were specified.

Table 8. Definitions of processes of care.

Processes of care	Definition	Time frame
Admission to a specialized stroke unit.	Admission to a hospital department/unit that exclusively or primarily is dedicated to patients with stroke and which is characterized by multidisciplinary teams, a staff with a specific interest in stroke, involvement of relatives, and continuous education of the staff.	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.
Examination with CT/MRI scans.		First day of hospitalization.
Assessment by a physiotherapist/occupational therapist.	Formal bed-side assessment of the patient's need for rehabilitation.	Second day of hospitalization.
Assessment of nutritional risk.	Assessment following the recommendations of the European Society for Parenteral and Enteral Nutrition; i.e., calculation of a score that accounts for both the nutritional status and the stress induced by the stroke.	Second day of hospitalization.
Early assessment of swallowing function.	Assessment according to the Gugging Swallowing Screen.	First day of hospitalization.
Early mobilization.	Nurse or physio/occupational therapy team performing mobilization and out-of-bed (sitting, standing or walking).	First day of hospitalization.

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 another diagnosis. The discharge date was defined somewhat differently in the two study areas: in the former Copenhagen Hospital Corporation, the date was defined as the date of discharge from the stroke unit either to a rehabilitation ward, home, a nursing home, or death. In the former Aarhus County, LOS also included transfers to rehabilitation wards and therefore covered the entire hospital stay.

Mortality

A main ***outcome*** in *Study III* was death from any cause after 30 days and one year**.** The mortality was ascertained from the Civil Registration System.

Confounding factors

A number of factors may affect the outcome after stroke. We therefore adjusted for a wide range of potential confounding factors in studies II and III. Data on the potential confounding factors were obtained through the different Danish registries.

- *Comorbidity*

To adjust for confounding by comorbidity in studies II and III, we computed for each patient the Charlson comorbidity index score (CCI) developed by Charlson et al[165] (Appendix III) based on discharge diagnoses from the Danish National Patient Registry. The index covers 19 major disease categories, including diabetes mellitus, myocardial infarction, heart failure, cerebrovascular diseases, and cancer, weighted according to their effect on patient survival, and is widely used to control for confounding in epidemiological studies. Further, it has been reported to be useful for patients with stroke.[166] Recently, the PPV of the included disease diagnoses, as ascertained in the NRP, was found to be very high.[167]

We calculated the score based on all previous discharge diagnoses recorded before the date of admission but excluded discharge diagnoses of cerebrovascular diseases. We defined three comorbidity levels on the basis of the CCI score: 0 (“low”), corresponding to patients with no recorded underlying diseases according to the CCI score; 1–2 (“medium”); and ≥3 (“high”). Furthermore, we adjusted for previous and/or current atrial fibrillation and hypertension.

- *Patient characteristics*

We also adjusted for in-hospital processes of care and patient characteristics known to be associated with stroke outcome, including age, sex, marital status, housing, profession, smoking habits, alcohol intake, type of stroke, and severity of stroke.

Statistical analyses

All data were analyzed using STATA® (StataCorp, College Station, Texas, USA) (version 10.0 in studies I and II, and version 11.0 in Study III). For all estimates, a 95% CI was calculated. The studies were approved by the Danish Data Protection Agency (J.no.2007-41-0563) and Study I also by the National Board of Health (J.no.7-604-04-2/26/EHE).

Descriptive analysis

Characteristics of the populations in the three study groups were described using proportions, median, and quartiles.

Positive and negative predictive values, the sensitivity, and the specificity (Study I)

In Study I, positive and negative predictive values, the sensitivity, and the specificity were calculated for all complications combined and for the specific complications (pneumonia, UTI, pressure ulcer, falls, DVT, PE, and constipation) (Table 9). Finally, we estimated the proportion of patients who had at least one symptom of a complication registered in their medical record among patients registered in the DNIP with the complication[168]

Table 9. A two-by-two table illustrating evaluation of the data validity in the two registries

		Complication according to gold standard: medical record	
		Yes	No
"Test" Registry e.g. DNIP	Yes	True positive	False positive
	No	False negative	True negative

$$\text{Sensitivity} = \frac{\text{true positives}}{\text{true positives + false negatives}}$$

$$\text{Specificity} = \frac{\text{true negatives}}{\text{true negatives + false positives}}$$

$$\text{PPV} = \frac{\text{true positives}}{\text{true positives + false positives}}$$

$$\text{NPV} = \frac{\text{true negatives}}{\text{true negatives + false negatives}}$$

The positive and negative predictive values of the registered complications in the DNIP and the NRP were assessed using the review of the medical records as the gold standard. PPV values of the complications in the registries were computed as proportions with the numerator being the number of patients with a verified complication, after review of medical records using the diagnostic criteria in Appendix II, and the denominator being the total number of patients registered in the DNIP/NRP with this specific complication. Negative predictive values (NPVs) of the complications in the registries were computed as proportions with numerator being the number of patients verified to not have the specific complication, after review of medical records using the diagnostic criteria in Appendix II, and the denominator being the total number of patients registered in the DNIP/NRP without this specific complication. We computed the sensitivity of the complications as the proportion of patients with a verified complication registered in the DNIP/NRP divided by the total number of patients in our random sample with a complication in the medical record. Specificity of the complications was similarly defined as the number of patients without any verified complication registered in the DNIP/NRP divided by the total number of patients in our random sample without a complication in the medical record.

Logistic regression (Study II)

The association between specific processes of care and the risk of the individual medical complications in Study II was expressed as crude and adjusted OR. Data were analyzed using logistic regression with adjustment for all of the above-mentioned patient characteristics. In the analyses of specific processes of care, there was also mutual adjustment for the remaining processes of care. Age and SSS score were included as natural cubic splines. In all of the analyses, we corrected for clustering of patients by department, because unmeasured characteristics of the department, including other aspects of care other than the processes examined in this study, could be associated with medical complications. The Wald test was used to test for trends in the association between the proportion of relevant processes of care received and the individual medical complications. Patients were included in the analyses only if they had no contraindications, and were considered eligible for the specific processes of care and the LOS was >0.

The 95% CIs were calculated using robust estimates of the variance that allowed for clustering of patients by stroke units.[169]

Linear regression (Study III)

The association between the individual medical complication (exposure) and LOS (outcome) was expressed as ratios of the median LOS (unadjusted /adjusted) and derived from a linear regression.

The 95% CIs were calculated using robust estimates of the variance that allowed for clustering of patients by stroke units.
A natural log (ln) transformation was used to correct for the right skewness of LOS.[170] When reporting the findings of the analyses, we transformed the regression estimates back into the original units by exponentiating the estimates, and thus obtained the ratios of the geometric means of LOS values.

Cox proportional hazards regression analysis (Study III)

The associations between the specific medical complication and the risk of death in Study III were expressed as morality rate ratios (MRR), which were derived from a Cox proportional hazards regression analysis. Follow-up started on day of hospital admission date and ended after 30 days, one year, the end of the study period or date of emigration, whichever came first.
We adjusted for all of the above-mentioned patient characteristics. Age and SSS score were included as natural cubic splines. We used a random-effects model to correct for possible clustering by department in all analyses.[169]
We also constructed cumulative mortality curves for the presence of one or more complications ("any complication") compared to none, and assessed the assumption of proportional hazards in the Cox regression model using log(-log(survival)) plots.

Sub analysis /sensitivity analyses

To evaluate the robustness of our findings in studies II and III, we first stratified the analyses according to age, sex, and SSS score to assess whether these acted as effect modifiers on the association between Study II: processes of care and medical complications and Study III: medical complications and LOS or mortality. Second, in Study III, we replicated the analyses of LOS stratified by discharge status (dead/alive at discharge) and according to geographic area (Copenhagen or Aarhus).

Multiple imputation (studies II and III)

In studies II and III 52.4% (n=6.157) and 51.25% (n =7,032), respectively, of the patients had missing data on one or more of the following variables: marital status, housing, profession, alcohol intake, smoking habits, atrial fibrillation, hypertension, history of previous stroke, SSS and ranking score. Because exclusion of all patients with missing data would have reduced the sample size substantially and potentially also introduced a selection bias, we used multiple imputation to impute missing values of the patient characteristics assuming that data were missing at random.[171,172] We imputed five datasets using the following variables: age, sex, marital status, housing, profession at admission, alcohol intake, smoking habits, atrial fibrillation, hypertension, SSS score, preadmission modified Rankin score, the CCI score, previous stroke, stroke subtype, stroke unit identifier, proportion of relevant processes of care received, and combined results obtained from each. The OR/MRR values were then averaged across the five imputations, correcting for between- and within-imputation variation.[171]

In Study III, in addition to all measured covariates, we included the event indicator and the Nelson-Aalen estimator of the cumulative hazard to the survival time in the imputation model.[173]

RESULTS

The main results of the three studies are summarized below.

Summarizing the whole study period 2003–2009 (Study III) a total of 13,721 patients were eligible for analysis, of which a total of 25.2 % (*n* =3,453) experienced at least one medical complication during their hospitalization. The most frequent complications were UTI (15.4%), pneumonia (9.0%), and constipation (6.8%) (Table10).

Median LOS was 13 days (25th and 75th quartiles: 5, 33). Although the number of patients differed in the three study periods /studies the above-mentioned percentages were very much alike in all three studies with differences between 0.0–0.6 percentage points for the variables mentioned.

Table 10. The cumulative risk of medical complications in DNIP 2003–2009.

	The Danish National Indicator Project		
Medical complication	**Yes % (N)**	**No % (N)**	**Unknown % (N)**
Pneumonia	9.0 (1,235)	80.6 (11,055)	10.4 (1,431)
Urinary tract infection	15.4 (2,107)	74.1 (10,164)	10.6 (1,450)
Pressure ulcer	1.2 (163)	88.9 (12,194)	9.9 (1,364)
Falls after stroke	2.1 (288)	87.6 (12,021)	10.3 (1,412)
Venous thromboembolismn	0.6 (86)	89.2 (12,240)	10.2 (1,395)
Constipation	6.8 (935)	82.1 (11,260)	11.1 (1,526)
Overall (Complication Yes/No	25.2 (3,453)	66.1 (9,075)	8.7 (1,193)

Study I

In Study I we found substantial diagnosis- and register-specific variation when validating the data quality of seven stroke-related medical complications registered in public Danish registries.

The PPVs and NPVs were generally moderate to high for most complications in the two registries. Table 11 presents the PPVs and NPVs of all the reviewed medical complications in the DNIP and NRP. The PPVs ranged from 39.0% (95% CI: 24.2–55.5) for pressure ulcer to 87.1% (95% CI: 78.0 –93.4) for pneumonia in the DNIP, and from 0.0% (95% CI: 0.0– 97.5) for falls to 92.9% (95% CI: 66.1–99.8) for pneumonia in the NRP. The NPVs ranged from 71.6% (95% CI: 67.2–75.7) for pneumonia to 98.9% (95% CI: 97.5–99.6) for PE in the DNIP and from 63.3% (95% CI: 59.2–67.3) for pneumonia to 97.4% (95% CI: 95.8–98.5) for PE in the NRP.

In addition, the specificity of the medical complication diagnoses was high for all complications in the two registries. The specificity ranged from 93.7% (95% CI: 91.0–95.8) for constipation to 99.8% (95% CI: 98.9–100.0) PE in the DNIP, and from 98.0 (95% CI: 96.1–99.1) for UTI to 100% (95% CI: 99.9–100.0) for PE in the NRP. In contrast, major differences were found in the two registries for the sensitivity of the medical complication diagnoses. The sensitivity for all types of complications was moderate to low in the DNIP, whereas it was extremely low in the NRP. The sensitivity ranged from 23.5% (95% CI: 14.9– 35.4) for falls to 62.9% (95% CI: 54.9–70.4) for UTI in the DNIP, and from 0.0 (95% CI: 0.0–4.99) for falls to 18.1% (95% CI: 2.3–51.8) for pressure ulcer in the NRP (Table 12).

Table 11. Positive and Negative Predictive Values for all the reviewed medical complications in the Danish National Indicator Project and the National Registry of Patients.

	The Danish National Indicator Project				The National Registry of Patients			
Medical complication	**Verified N/total N**	**PPV % (95% CI)**	**Total negative N/total N**	**NPV % (95% CI)**	**Verified N/total N**	**PPV % (95% CI)**	**Total Negative N/total N**	**NPV % (95% CI)**
Pneumonia	74/85	87.1 (78.0 –93.4)	330/461	71.6 (67.2–75.7)	13/14	92.9 (66.1–99.8)	364/575	63.3 (59.2–67.3)
Urinary tract infection	122/149	81.9 (74.7–87.7)	340/399	85.2 (81.3–88.5)	30/39	76.9 (60.7–88.9)	390/550	70.9 (66.9–74.7)
Pressure ulcer	16/41	39.0 (24.2–55.5)	498/506	98.4 (96.9–99.3)	4/8	50 (15.7– 84.3)	561/581	96.6 (94.7–97.9)
Falls after stroke	35/47	74.5 (59.7–86.1)	444/496	89.5 (86.5–92.1)	0/1	0.0 (0.0–97.5)	497/588	84.5 (81.3–87.4)
Deep vein thrombosis	20/28	71.4 (51.3–86.8)	521/524	99.4 (98.3–99.9)	7/8	87.5 (47.3–99.7)	564/581	97.1 (95.4–98.3)
Pulmonary embolism	17/26	65.4 (44.3–82.8)	520/526	98.9 (97.5–99.6)	10/11	90.9 (58.7–99.8)	563/578	97.4 (95.8–98.5)
Constipation	46/84	54.8 (43.5– 65.7)	416/450	92.4 (89.6–94.7)	3/7	42.9 (9.9–81.6)	493/582	84.7 (81.5–87.5)
Overall	330/460	71.7 (67.4–75.8)	3069/3362	91.3 (90.3–92.2)	67/88	76.1 (75.9–84.6)	3432/4035	85.1 (83.9–86.1)

Table 12. Sensitivity and specificity of the medical complications in the Danish National Indicator Project and the National Registry of Patients

	The Danish National Indicator Project				The National Registry of Patients			
Medical complication	**Verified positive /total N**	**Sensitivity % (95% CI)**	**Verified negative /total N**	**Specificity % (95% CI)**	**Verified positive /total N**	**Sensitivity % (95% CI)**	**Verified negative /total N**	**Specificity % (95% CI)**
Pneumonia	51/182	28.0 (21.6–35.1)	330/339	97.3 (95.0–98.8)	12/201	6.0 (3.1–10.2)	362/363	99.7 (98.5–100)
Urinary tract infection	100/159	62.9 (54.9–70.4)	340/364	93.4 (90.3–95.7)	24/168	14.3 (9.4–20.5)	388/396	98.0 (96.1–99.1)
Pressure ulcer	3/11	24.4 (6.02–61.0)	498/511	97.5 (95.7–98.6)	2/11	18.11 (2.3–51.8)	550/553	99.5 (98.4–99.9)
Falls after stroke	16/68	23.5 (14.9–35.4)	444/450	98.7 (97.1–99.5)	0/72	0 (0–4.99)	491/492	99.8 (98.9–100)
Deep vein thrombosis	2/5	40.0 (5.27–85.3)	521/525	99.2 (98.1–99.8)	1/6	16.7 (0.4–64.1)	561/561	100 (99.3–100)
Pulmonary embolism	0/6	-	520/521	99.8 (98.9–100)	0/8	-	556/556	100 (99.9–100)
Constipation	31/65	47.7 (35.1–60.5)	416/444	93.7 (91.0–95.8)	3/77	3.9 (0.8–11.0)	484/487	99.4 (98.2–99.9)
Overall	203/496	40.9 (36.6–45.4)	3069/3154	97.3 (96.7–97.8)	42/543	7.7 (5.6–10.3)	3392/3408	99.5 (99.2–99.7)

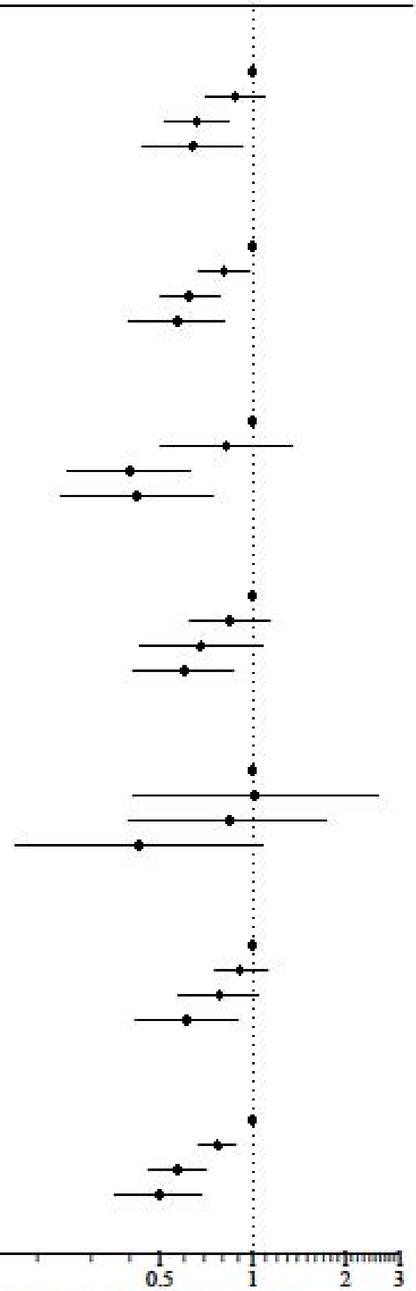
[a] Based on a 5% random sample of all patients registered in the study period.

Study II

We found that higher quality of care, characterized by early intervention during the acute phase of stroke, was associated with a lower risk of medical complications during hospitalization. The association remained after adjustment for a wide range of possible confounding factors and appeared to follow a dose-response relationship in all of the subgroups that we examined.
The lowest risk of complications was found among patients who received all relevant processes of care compared to patients who failed to receive any of the processes (i.e., adjusted OR ranged from 0.42 (95% CI: 0.24–0.74) for pressure ulcer to 0.64 (95% CI: 0.44–0.93) for pneumonia) (Figure 6). Table 13 shows adjusted ORs according to the specific processes of care received.
Compliance with six of the nine processes of care appeared to be associated with a lower risk for one or more medical complications (adjusted OR 0.43–0.97), although not all of the associations were statistically significant. Early CT/MRI scans and assessment by a physiotherapist or an occupational therapist were associated with an increased risk of any complication (adjusted OR: 1.10–1.52).
Of the individual processes of care, early mobilization was associated with the lowest risk of complications (i.e., adjusted OR ranged from 0.43 (95% CI: 0.34–0.54) for pneumonia to 1.01 (95% CI: 0.57–1.78) for VTE). However, early initiation of oral anticoagulant therapy was also associated with a significantly reduced risk of pneumonia, VTE, and constipation; adjusted ORs were 0.64 (95% CI: 0.46–0.89), 0.17 (95% CI: 0.05–0.55), and 0.52 (95% CI: 0.33–0.81), respectively.

Figure 6. Medical complications after admission for stroke according to proportion of received relevant processes of care.

Medical complications	Adjusted OR* (95% CI)
Proportion of processes of care	**Pneumonia**
0–24 %	1.00 (reference)
25–49 %	0.88 (0.70–1.10)
50–74 %	0.66 (0.52–0.83)
75–100 %	0.64 (0.44–0.93)
Test for trend	**p< 0.001**
Proportion of processes of care	**Urinary tract infection**
0–24 %	1.00 (reference)
25–49 %	0.81 (0.67–0.98)
50–74 %	0.62 (0.50–0.78)
75–100 %	0.57 (0.40–0.81)
Test for trend	**p< 0.001**
Proportion of processes of care	**Pressure Ulcer**
0–24 %	1.00 (reference)
25–49 %	0.82 (0.50–1.35)
50–74 %	0.40 (0.25–0.63)
75–100 %	0.42 (0.24–0.74)
Test for trend	**p< 0.001**
Proportion of processes of care	**Falls after stroke**
0–24 %	1.00 (reference)
25–49 %	0.84 (0.63–1.14)
50–74 %	0.68 (0.43–1.07)
75–100 %	0.60 (0.41–0.87)
Test for trend	**p = 0.019**
Proportion of processes of care	**Venous tromboembolism**
0–24 %	1.00 (reference)
25–49 %	1.02 (0.41–2.54)
50–74 %	0.84 (0.40–1.74)
75–100 %	0.43 (0.17–1.07)
Test for trend	**p = 0.145**
Proportion of processes of care	**Constipation**
0–24 %	1.00 (reference)
25–49 %	0.91 (0.75–1.11)
50–74 %	0.78 (0.58–1.05)
75–100 %	0.61 (0.42–0.90)
Test for trend	**p = 0.097**
Proportion of processes of care	**Any medical complication**
0–24 %	1.00 (reference)
25–49 %	0.77 (0.67–0.88)
50–74 %	0.57 (0.46–0.70)
75–100 %	0.50 (0.36–0.68)
Test for trend	**p< 0.001**



* All the analyses are corrected for clustering of patients by department and for age, sex, marital status, housing, profession, alcohol intake, smoking habits, atrial fibrillation (except for criteria on antiplatelet and anticoagulant therapy), previous stroke, Charlson Comorbidity Index, Scandinavian Stroke Scale Score on admission and fulfillment of one or more of the other quality of care criteria.

Table 13. Medical complications after admission for stroke according to individual processes of care received.

	Pneumonia	UTI	Pressure ulcer	Falls after stroke	VTE	Constipation	Any complication
Processes of care received	**Adjusted OR* (95% CI)**	**Adjusted OR* (95% CI)**	**Adjusted OR * (95% CI)**	**Adjusted OR * (95% CI)**	**Adjusted OR * (95% CI)**	**Adjusted OR * (95% CI)**	**Adjusted OR * (95% CI)**
Early admission to a stroke unit	0.81 (0.66–100)	0.84 (0.69–1.01)	0.90 (0.50–1.60)	0.92 (0.75–1.13)	1.20 (0.54–2.66)	0.92 (0.78–1.08)	0.79 (0.68–0.92)
Antiplatelet therapy	0.88 (0.66–1.17)	0.94 (0.81–1.08)	1.01 (0.55–1.87)	0.99 (0.60–1.63)	0.85 (0.44–1.63)	1.20 (0.91–1.59)	0.95 (0.79–1.15)
Anticoagulant therapy	0.64 (0.46–0.88)	0.79 (0.57–1.10)	0.90 (0.50–1.62)	0.47 (0.20–1.11)	0.17 (0.05–0.55)†	0.52 (0.33–0.81)	0.59 (0.45–0.76)
Examination with CT/MRI scan	1.51 (1.20–1.91)	1.37 (1.18–1.58)	0.92 (0.61–1.39)	1.51 (1.22–1.88)	1.28 (0.80–2.07)	1.48 (1.23–1.77)	1.52 (1.35–1.72)
Assessment by a physiotherapist	1.15 (0.95–1.39)	1.04 (0.92–1.17)	0.94 (0.66–1.32)	0.93 (0.68–1.26)	1.06 (0.76–1.49)	1.05 (0.84–1.30)	1.10 (0.94–1.28)
Assessment by an occupational therapist	1.12 (0.89–1.41)	1.05 (0.89–1.24)	0.95 (0.71–1.27)	0.98 (0.79–1.21)	1.26 (0.86–1.86)	1.12 (0.89–1.40)	1.10 (0.94–1.27)
Assessment of nutritional risk	0.90 (0.74–1.10)	0.96 (0.81–1.14)	1.08 (0.69–1.70)	0.70 (0.47–1.05)	0.64 (0.29–1.44)	0.83 (0.64–1.09)	0.87 (0.70–1.07)
Swallowing assessment	0.95 (0.79–1.15)	0.96 (0.76–1.20)	1.16 (0.84–1.60)	0.95 (0.69–1.31)	0.47 (0.19–1.19)	1.00 (0.75–1.34)	0.97 (0.84–1.11)
Early mobilization	0.43 (0.34–0.54)	0.56 (0.47–0.66)	0.43 (0.22–0.84)	0.88 (0.70–1.12)	1.01 (0.57–1.78)	0.45 (0.37–0.56)	0.43 (0.35–0.53)

*All analyses are corrected for clustering of patients by department and age, sex, marital status, housing, profession, alcohol intake, smoking habits, atrial fibrillation (except for criteria on antiplatelet and anticoagulant therapy), previous stroke, Charlson comorbidity index, Scandinavian stroke scale score on admission, and other processes of care received.

†Estimates not adjusted for alcohol intake and Charlson comorbidity index due to few outcomes.

Study III

We found that medical complications were significantly associated with an increased LOS and for some complications also with an increased 30-day and 1-year mortality.

Table 14 shows that the association for increased LOS remained after adjusting for a wide range of possible confounding factors including proportion of relevant processes of care received and correction for clustering of patients by department. Adjusted relative LOS ranged from 1.80 (95% CI: 1.54–2.11) for pneumonia to 3.06 (95% CI: 2.67–3.52) for falls after stroke.

Table 14. Medical complications and LOS.

Medical complication	N (%)	Median LOS (25th and 75th quartiles) Complication respectively = No	Median LOS (25th and 75th quartiles) Complication respectively = Yes	Unadjusted Ratio of LOS (95% CI)	Adjusted Ratio of LOS* (95% CI)
Pneumonia	1,235 (9.0)	11 (4, 28)	31 (14, 60)	2.41 (1.91–3.05)	1.80 (1.54–2.11)
Urinary tract infection	2,107 (15.4)	10 (4, 25)	36 (16, 64)	3.12 (2.25–4.32)	2.29 (1.88–2.80)
Pressure ulcer	163 (1.2)	13 (5, 32)	48 (26, 74)	3.34 (2.20–5.06)	1.98 (1.53–2.55)
Falls after stroke	288 (2.1)	12 (5, 31)	56 (31, 86)	4.33 (3.24–5.78)	3.06 (2.67–3.52)
Venous thromboembolism	86 (0.6)	13 (5, 32)	56 (25, 99)	3.73 (2.65–5.25)	2.40 (1.96–2.95)
Constipation	935 (6.8)	11 (5, 28)	45 (25, 73)	3.80 (.2.82–5.11)	2.66 (2.23–3.16)
Any complication	3,453 (25.2)	9 (4, 21)	33 (15, 62)	3.29 (2.45–4.14)	2.48 (2.01–3.06)

*All analyses are corrected for clustering of patients by department and age, sex, marital status, housing, profession, alcohol intake, smoking habits, atrial fibrillation, previous stroke, hypertension, Charlson comorbidity index, Scandinavian stroke scale score on admission, type of stroke, and relevant processes of care received.

Figure 7 shows that patients who experienced at least one of seven complications had an increased mortality after one year compared with patients who did not experience any of the complications. This association remained after adjusting for possible confounding factors adjusted 1-year MRR: 1.20 (95% CI: 1.04–1.39).

The overall 30-day mortality rate was 8.9%, and the overall 1-year mortality rate was 21.0 %.

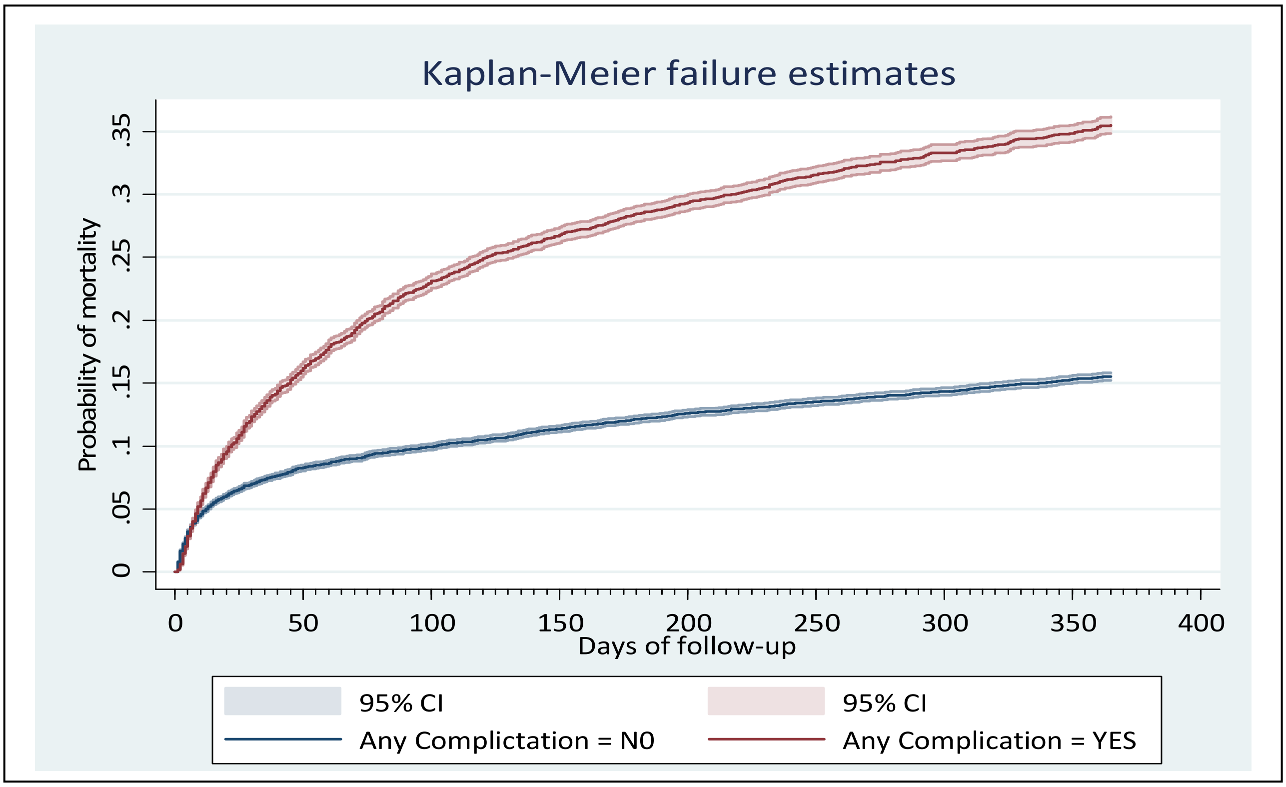


Figure 7. Cumulative mortality curves of 1- year all-cause mortality after hospitalization with acute stroke among patients with and without in-hospital medical complications.

Table 15 shows adjusted MRR values according to the individual medical complication. The presence of pneumonia and VTE was associated with higher 30-day mortality although the association did not reach statistical significance in the case of VTE. The adjusted OR's were 1.59 (95% CI: 1.31–1.93) and 1.49 (95% CI: 0.75–2.96), respectively. UTI, falls after stroke, and constipation were all associated with a significantly lower risk of 30-day mortality (adjusted MRR 0.21–0.74), whereas the MRR for pressure ulcer was not statistically significant.

The highest 1-year mortality rate was found among patients with pressure ulcer and pneumonia (adjusted MRR 1.47 (95% CI: 1.17–1.85) and MRR 1.76 (95% CI: 1.45–2.14), respectively). The presence of complications like UTI, falls after stroke, and constipation was associated with a decrease in 1-year mortality.

Table 15. Medical complications and 30-day and 1-year all cause mortality.

Medical complication	N (%)	30-day mortality rates			1-year mortality rates		
		30-day mortality N (%)	Unadjusted MRR (95% CI)	Adjusted MRR * (95% CI)	1-year mortality N (%)	Unadjusted MRR* (95% CI)	Adjusted MRR* (95% CI)
Pneumonia	1,235 (9.0)	307/1218 (25.2)	4.43 (3.57–5.50)	1.59 (1.31–1.93)	628/ 2,886 (21.8)	4.07 (3.43–4.80)	1.76 (1.45–2.14)
Urinary tract infection	2,107 (15.4)	153/1218 (12.6)	0.88 (0.69–1.12)	0.45 (0.38–0.54)	669/ 2,886 (23.2)	1.91 (1.73–2.11)	0.94 (0.84–1.05)
Pressure ulcer	163 (1.2)	22/1218 (1.8)	1.64 (1.03–2.62)	0.74 (0.42–1.30)	88/ 2,886 (3.1)	3.20 (2.62–3.90)	1.47 (1.17–1.85)
Falls after stroke	288 (2.1)	76/1218 (0.6)	0.27 (0.13–0.56)	0.21 (0.10–0.47)	68/ 2,886 (2.4)	1.11 (0.99–1.25)	0.82 (0.68–0.99)
Venous thromboembolism	86 (0.6)	15/1218 (1.2)	2.24 (1.30–3.84)	1.49 (0.75–2.96)	30/ 2,886 (1.0)	1.93 (1.14–3.29)	1.28 (0.71–2.29)
Constipation	935 (6.8)	45/1218 (3.7)	0.54 (0.35–0.83)	0.38 (0.28–0.50)	260/ 2,886 (9.0)	1.41 (1.18–1.69)	0.87 (0.76–0.99)
Any complication	3,453 (25.2)	426/1218 (35.0)	1.79 (1.40–2.29)	0.78 (0.65–0.95)	1,201/ 2,886 (41.6)	2.53 (2.18–2.95)	1.20 (1.04–1.39)

*All analyses are corrected for clustering of patients by department and age, sex, marital status, housing, profession, alcohol intake, smoking habits, atrial fibrillation, previous stroke, hypertension, Charlson comorbidity index, Scandinavian stroke scale score on admission, type of stroke, and proportion of relevant processes of care received.

DISCUSSION

Methodological considerations

Before deciding whether an association is causal, it is necessary to consider whether the association may be an artifact arising from bias or random variation. The association also might be indirect through another (confounding) factor. In all observational studies, systematic errors due to the lack of randomization may affect the validity of our findings. We must therefore critically evaluate alternatives to causal interpretation before interpreting the findings as evidence of causality. Specifically, we need to consider how problems in selection and information, confounding factors, and statistical imprecision may have influenced our estimates (Figure 8).[168]

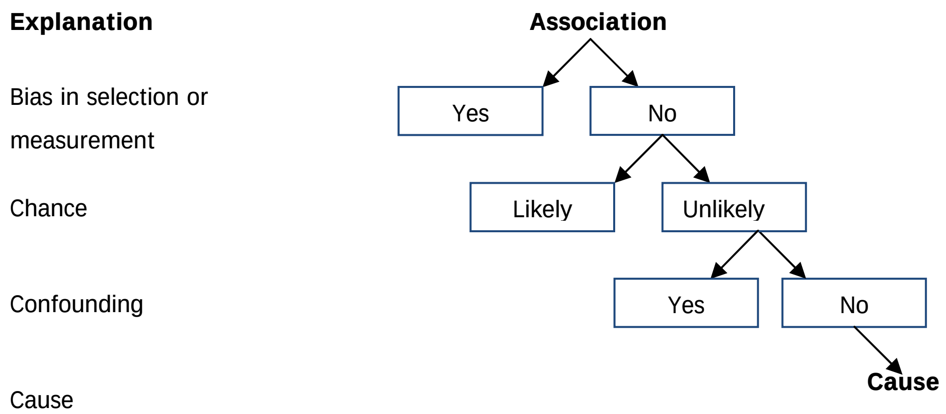


Figure 8. Association and cause.[168]

We can consider causal inference only when these alternative explanations can be excluded, or at least thought of as being of only minor importance.

In this section, the issues of selection and information problems, confounding, and statistical precision are discussed for studies I–III. Please note that Study I is not a conventional analytical epidemiological study and that a thorough discussion of all of these issues is not applicable for this study.

Selection problems

Selection problems include selection mechanisms that may occur during sampling of the study subjects and selection biases.[174] Selection problems may thus influence both the external and the internal validity of a study. Selection problems might have been introduced at different levels of this study, (i.e. when sampling the study population or during identification of the cases).

All studies in this thesis used a nationwide population-based registry that enabled valid identification of the study population independently of the study hypothesis. The study population consisted of patients with acute stroke who had been admitted to the 10 dedicated stroke units in the former Copenhagen Hospital Corporation and Aarhus County, registered in the DNIP. Participation in DNIP is mandatory for all departments in Denmark treating patients with acute stroke, and extensive efforts are made to ensure the validity of DNIP data:[163]

- DNIP is established as a concerted action among a number of Danish institutions, including the Ministry of Health, the National Board of Health and the health professions in coordination with scientific societies.
- There is a nationwide project organization with ramifications for all the participating departments, and detailed written instructions of how to record data in the project, including specific inclusion and exclusion criteria, are available.
- A structured audit process is carried out regularly on a national, regional, and local basis to assess critically the quality of the dataset and results.
- To ensure completeness of patient registration in DNIP, its enrolees are compared with local hospital discharge registries taking into account local variation in coding praxis of discharge diagnoses.

The studies included only patients admitted to stroke units in the Copenhagen and Aarhus areas, which may have limited the generalizability of the findings to other settings, where the prevalence of complications and the diagnostic strategy may be different. However, the above-mentioned principles might indicate that the studies have a high external validity to the other stroke units in Denmark, as it should be expected that other units follow the same broad principles of care of patients with acute stroke. This might also be applicable in relation to populations in other countries that follow the same principles of care of patients with acute stroke as those used in Denmark.
In studies II and III, we limited the risk of bias from missing data by using multiple imputation to impute missing values.[172]

Loss to follow-up is always a potentially important source of selection bias in follow-up studies. Selection bias occurs when the loss to follow-up is related to both the risk of exposure and the outcome.

However, the above mentioned principles of DNIP are also likely to have minimized the risk of any systematic loss to follow-up in *Study II*.
In *Study III,* we used the Danish Civil Registration system to obtain data on vital status, and because this registry is considered highly accurate, we had in practice complete follow-up.

Information problems

Information bias may occur when there is systematic error in the measurement of exposure, outcome, or confounding factors. The measurement error is often referred to as misclassification for categorical variables. Misclassification can be either non-differential with the measurement error evenly distributed between comparison groups, or differential with an uneven distribution of the error among the comparison groups. Only differential misclassifications consistently lead to systematic over- or underestimation of the true association. Non-differential misclassification of a dichotomous exposure will most likely bias the association toward null. When more than two groups are compared, non-differential misclassification may lead to either an over-or underestimation of the association, depending on the categories into which the patients are misclassified.

Study I

In Study I, we had access to medical records with detailed clinical data. The review was based on all available information in the medical records, including written radiology reports, results from laboratory tests, and nurse records. The actual brain imaging films were not re-interpreted.
We used standardized evaluation of the records including the use of well-defined diagnostic criteria developed in accordance with available existing literature and/or international consensus which all together was aimed at minimizing information problems. Furthermore, all cases with uncertain diagnosis, based on the available information, were discussed with senior consultants.
However, the use of a single reviewer, not blinded to the diagnosis in the DNIP, to review the medical records was a potential methodological limitation because of the possibility of error in extracting information from the records. The use of retrospective review of medical records may also be a limitation because the collection and the quality of the data are not under control of the researcher (e.g., the required information to make a valid conclusion about the presence of specific medical complications was always available in the medical records).

Studies II and III

It is well known that misclassification can occur during data collection in routine clinical settings.

Although DNIP data on processes of care may have been subject to misclassification, such misclassification was probably independent of medical complications, LOS and mortality because of the study's prospective design. Such non-differential misclassification would lessen our ability to detect associations between the quality of care and medical complications and therefore produce more conservative risk estimates.
A low sensitivity would result in misleading rates in a study determining incidence (e.g., of medical complications among patients with stroke), whereas analytical studies examining associations would likely produce unbiased relative risk estimates because of the high specificity.[175] Thus, in analytical studies, a low specificity would be far more troublesome in most situations than a low sensitivity.[176] The fact that half of the complications not verified *(Study I)* had at least one or several symptoms of the specific complications registered in the medical record indicates that data on complications in the DNIP are valid, although the international criteria for the specific complication were not completely fulfilled.

In *Study III,* one of the outcomes was death. Information bias from errors in this outcome is unlikely because the deaths were recorded completely and independently of the medical complications by the Danish Civil Registration System. Similarly, information on LOS in DNIP is also virtually complete in the DNIP. However, it should be noted that LOS was defined somewhat differently in the Copenhagen and Aarhus areas: in Copenhagen it only included stay in the stroke unit, whereas transfers to in-hospital rehabilitation units were also included in the LOS registered in Aarhus. Still, this difference did not affect the overall conclusion as the estimates of relative LOS were comparable when stratifying the analyses according to geography.

Confounding

On the simplest level, confounding may be considered a confusion of effects. To act as a confounder in a study of, e.g., mortality in patients with stroke, a factor must (1) in itself be a risk factor for mortality, (2) be unevenly distributed between the comparison groups, and (3) not be a consequence of the exposure.[177]

Several precautions were taken to minimize the impact of possible confounding, including control for a wide range of well-established prognostic factors (e.g., stroke severity), as well as clustering at the individual stroke units. Nevertheless, our estimates may still be affected by residual confounding arising from either misclassification or use of crude categories for some of the included covariates, such as hypertension being reduced to yes/no and not including different levels of blood pressure or the use of the CCI score potentially leading to an imperfect adjustment for

comorbidity. The estimates may also have been affected by unmeasured factors such as blood glucose measurement and temperature or unknown confounding factors.
Furthermore, in S*tudy II,* only patients who were considered eligible for care by the staff were included in analyses of the specific processes of care, thereby minimizing the risk of confounding by indication, which occurs when "the indication" (the reason) that made a doctor prescribe, such as a drug, is also associated with the observed outcome.[168] Yet, residual confounding by indication may remain in some of the associations that we studied, as indicated by the apparent increased risk of complications associated with fulfilment of some of the processes of care.
Finally, in S*tudy III,* we did not take into account other factors that might predict outcome after discharge from hospital such as prescription of and compliance with discharge medications.

Chance: statistical precision

Random error or chance is inherent in all observations. We used 95% CIs throughout this thesis to report the precision of the estimates. The width of the CI's indicates the amount of random error in our estimates.

Although the number of reviewed medical records in *Study I* was relatively large compared to other validation studies based on detailed review of medical records, some of the complications (e.g., DVT and PE) were rare, with relatively few cases available for assessment. Consequently, the precision of the estimated predictive values, sensitivity, and specificity for these complications was only moderate.
To the best of our knowledge *Study II and Study III* are among the largest of studies on the topic to date, and because of their sizes, the statistical precision of the risk estimates was fair, as indicated by the relative narrow CI's seen for most of the risk estimates. Furthermore, the size made it possible to study the specific medical complications further. However, even in our large cohorts, there is a limited information on specific complications, where the incidence was low (e.g., diagnosed VTE) and the CIs were correspondingly broad. In addition, the limited number of events of some of the medical complications also made it difficult to ensure effective control for confounding at all times and complicated further additional analyses of subgroups divided by age, for example, into younger and older patients.

In conclusion the strengths of our studies are their sizes, the population-based design, detailed prospective data collection, and complete follow-up for ascertainment of survival status. In addition, only patients without registered contraindications for the specific processes of care were included in the analyses. Finally, detailed data were available on possible confounding factors.

Study limitations include the use of possibly inaccurate data collected during routine clinical work in a large number of settings and the risk of non-differential misclassification of the collected exposure and confounder data; the possibility of residual or unaccounted confounding and the moderate statistical precision of some of the risk estimates.

Comparison with the existing literature

Study I

Medical complications in patients with stroke: data validity in a stroke registry and a hospital discharge registry

To the best of our knowledge no other studies have validated the quality of diagnoses of medical complications among patients with stroke in administrative and clinical registries. Some studies have validated registry diagnoses of medical complications in different patient populations (e.g., unselected internal medicine patients, pregnant women, patients from geriatric wards, patients from general practice or with a former cancer diagnosis) (Table 3). Our findings of moderate to high PPVs in both registries are generally in accordance with the results from a number of these studies.[103-113]

The PPVs reported from previous studies have ranged from 20.7% for pressure ulcer to 96.2 % for pneumonia.[103-106,108-113] Only a few studies have previously reported the sensitivity and specificity of diagnoses of medical complications in registries. Quan et al. examined diagnoses of complications in Canadian administrative hospital discharge data and found that the sensitivity ranged from 0% to 57.1% (higher than 50% for only two conditions). In contrast, the specificity was generally high (range: 99.0–100%).[107] This outcome is very consistent with our findings and also in line with findings from validation studies on other diagnoses not related to medical complications.[176]

Study II

Processes of care and medical complications in patients with stroke

The cumulative risks of medical complications found in our study are in agreement with those of a number of other studies[35,43,48,52,57,67] (Table 1). However, we did find a lower risk of falls (2.5%) and constipation (7.0 %) than in most other studies in which the reported cumulative risk of falls ranges from 8.4% to 25%[35,36,38,40,49], (Table 1) and the risks of constipation range from 16% to 66% (Table 2).[43,69]

As presented in the Introduction, only sparse information is available on the association between specific processes of care and the risk of medical complications in patients with acute stroke. In line with our study findings, Kwan et al, in a Cochrane review that included three randomized and 12 nonrandomized studies, found that patient management with stroke care pathways was associated with a lower risk of developing certain complications, including UTIs.[126] Furthermore, Perry et al found that implementation of evidence-based guidelines for nutrition, including early assessment of nutritional risk and early assessment by a physiotherapist or an occupational therapist of acute stroke was associated with a significantly reduced risk of post-stroke pneumonia and UTI.[127]

Our findings regarding an increased risk of falling among patients who were mobilized early is in accordance with that of Czernuszenko et al.[55] Also in line with our results, Cuesy et al demonstrated in an RCT that early mobilization in the form of passive turning and mobilization used with patients during the acute phase of an ischemic stroke decreased the incidence of pneumonia.[125] The optimal timing of mobilization has so far been unclear, but mobilization within the first few days seems to be well tolerated and not harmful.[178] In agreement with this idea, our study confirms the importance of very early mobilization within the first post-admission day.

Overall, previous studies, like our findings, support the use of care pathways/processes of care in acute stroke care[136] and an early multidisciplinary effort to ensure optimal care to prevent medical complications.

Study III

Medical complications in patients with stroke and clinical outcome: LOS and mortality

LOS

The significantly longer LOS for patients with medical complications found in our study is in agreement with a number of studies (Table 5). In line with our findings, these previous studies generally found that infections particularly were associated with longer LOS. [59,63,98,145,146] Data are limited on the role of other types of medical complications including pressure ulcer, falls, DVT, PE, and constipation. However, our results identifying an increased LOS for patients experiencing falls agree with those of Czernuszenko et al, who found that the probability of experiencing a first fall increases with LOS.[55] Furthermore, in accordance with a Chinese study, we found that patients with constipation stayed longer in the hospital than those without constipation.[56]

Interpretation of observational data on complications and LOS is in general a challenge as pointed out in earlier studies, where medical complications were also associated with longer LOS among patients with acute stroke. [43,50,96] Thus, it is difficult with certainty to determine whether longer LOS is caused by medical complications or whether longer LOS caused the complications. This challenge is also present in our study and should be kept in mind when interpreting the findings. However, the fact that most of the medical complications appear to develop early after hospital admission supports the hypothesis that medical complications *per se* may increase LOS.[36]

Mortality

The increased risk of 30-day and 1-year mortality for some of the individual medical complications found in our study is in agreement with the findings of a number of studies. In line with our findings Bae et al found that patients with complications had a considerably higher 1- year mortality than did patients without complications.[37] Furthermore, in accordance with our findings, a number of existing studies found an increased risk of both short- and long-term morality in patients who have had an infection such as pneumonia.[38,43,44,57,59,67,68,70,98,100,148-150] Katzan et al found that pneumonia was a leading cause of death in the post-acute phase of stroke, accounting for approximately 30% of the 30-day mortality.[150] This result was confirmed by Heuschmann et al in a another large registry study that identified pneumonia as the complication with the highest attributable proportion of death in the entire stroke population, accounting for 31% of all in-hospital deaths.[68]

VTE was associated with a higher 30-day and 1-year mortality in our study, although it did not reach statistically significance. This result is partly in agreement with previous studies that have identified VTE as an important contributor to mortality in patients with stroke.[67,93]

Interestingly, we found UTI, falls, and constipation, to be associated with a lower 30-day mortality following stroke. A similar finding for UTI has earlier been reported in some[63,98] but not all previous studies[48,53,68,70], whereas data on the remaining complications have been missing. The findings are to some extent in line with a study that indicated that stroke unit care appeared to reduce the risk of death attributable to complications of immobility.[157] The explanation for this is not entirely clear, but the findings indicate that stroke units are effective settings for detecting and treating medical complications at an early stage. Patients with complications could possibly also receive an even closer monitoring during the remaining part of their hospitals stay which could contribute to the lower mortality compared to patients without the mentioned medical complications. This observation adds to our understanding of the stroke units. It has though been known for many years that stroke unit care reduces the risk of death after stroke, but how this benefit is achieved, is unclear. It has been suggested that some of the survival benefit of stroke unit care may be explained by a reduction in the risk of complications,[128] and by earlier initiation of rehabilitation[128], and mobilization and by careful monitoring of clinical parameters[99,179,180] Effective treatment of medical complication should maybe also be added to the list, although a more firm conclusion on this topic would require a formal comparison with stroke patients not admitted to stroke units.

MAIN CONCLUSIONS

Study I

We found moderate to high predictive values for medical complication diagnoses among patients with stroke in two population-based registries. However, the sensitivity varied substantially between the two registries, with the stroke registry having a much higher sensitivity compared to the hospital discharge registry. The specificity of the diagnoses was high in both registries. These findings indicate that data from the DNIP may be useful for studying medical complications in patients with stroke, particularly for analytical studies.

Study II

We found that a range of processes of care in the acute phase of stroke, defined by receiving specific relevant processes of care, was associated with a substantially lower risk of medical complications in a large population-based follow-up study. The association between the number of relevant processes of care received and medical complications appeared to follow a dose-response pattern. The lowest risk of complications was found among patients who received all relevant processes of care compared to patients who failed to receive any of the processes. Of the specific processes of care, early mobilization was associated with the lowest risk of medical complications.

Study III

We found that patients hospitalized with medical complications had significantly longer LOS than did patients without complications. In-hospital complications were also in particular for pneumonia associated with an increased mortality.

PERSPECTIVES

"I never think of the future – it comes soon enough." Albert Einstein (1879–1955).

Unlike Einstein, we have to think of the future and plan now to reduce the numbers of deaths and rate of disability from stroke,[14] as the already high burden and costs of stroke are estimated to increase further because of an ageing population and a growing epidemic of diabetes, obesity, and physical inactivity among the general population. In the future, increased emphasis needs to be placed on the appropriate use of proven treatments for everyone with stroke.[14]

In this thesis we found strong support for the hypothesis that offering recommended processes of care in the acute phase of stroke, in particular early mobilization may prevent medical complications. This finding emphasizes that early appropriate multidisciplinary treatment is a mainstay in stroke treatment.

The Danish national healthcare system provides an optimal setting for conducting large population-based studies of stroke. The civil registration numbers make it possible to unambiguously link medical databases and administrative registries and thereby build large cohorts with detailed longitudinal data that include complete hospital history, comorbidity data, and complete long-term follow-up data. Our studies have, however, also exposed some of the weaknesses in the Danish healthcare databases. We found the sensitivity varied substantially between the two registries with the stroke registry having a much higher sensitivity compared to the hospital discharge registry. Another main weakness is the lack of clinical data in the hospital discharge registry. The studies presented in this thesis demonstrate that the DNIP constitutes a potentially valuable tool for further investigation of a number of issues concerning medical complications in patients with stroke. The databases linkages may be an effective and appropriate method to extend the usability of the DNIP data and should be further used (a) to determine the risk factors/ predictors for developing medical complications including demographic, socioeconomic and clinical factors and (b) to further examine the consequences of medical complications on a wider range of outcomes, including patient-reported outcome measures and healthcare utilization.

More data are clearly needed in order to better understand and further improve stroke unit care. This includes further studies on the association between specific processes of care and medical complications, preferably RCTs on the efficacy of specific interventions (e.g., prophylactic use of antibiotics and different durations and intensities of rehabilitation), which may further improve recovery for patients with stroke. More knowledge about the care pathways and patient outcomes following hospital discharge is also strongly needed. Thus, little is known about how best to ensure that patients, who have experienced in-hospital medical complications, are not re-admitted with new complications after hospital discharge.

However, although this thesis supports that the Danish clinical stroke database DNIP already has a number of strong features, the DNIP should continuously be developed and updated to ensure its long-term relevance and usefulness.

SUMMARY

Stroke is of major importance for public health internationally as well as in Denmark because it ranks as the third most common cause of death and the most frequent cause of serious functional impairment in the adult population. Patients hospitalized with stroke frequently experience medical complications such as pneumonia, urinary tract infection, pressure ulcer, falls, venous thromboembolism, and severe constipation. It has been indicated that there could be an association between medical complications and poorer outcome in patients with stroke because complications may hinder optimum rehabilitation and extend length of stay and have been associated with increased mortality. However, the available data on incidence, causes, and consequences of serious medical complications are sparse and inconclusive.

This thesis is based on a data validation study and two follow-up studies conducted in the former Copenhagen Hospital Corporation and Aarhus County, Denmark, and are based on data from the Danish National Indicator Project, the Civil Registration System, the Danish National Registry of Patients, and medical records. The aims were to examine (1) the validity of data regarding medical complications registered in two population-based Danish registries among patients hospitalized with stroke, (2) the association between processes of care and the risk of medical complications, and (3) the impact of in-hospital medical complications on (a) length of stay and (b) the 30-day and 1-year mortality.

Summarizing the whole study period 2003–2009 (Study III) a total of 13,721 patients were eligible for analysis, and of these which every fourth patient hospitalized with acute stroke (25.2%, n =3,453) experienced at least one medical complication during their hospitalization. The most frequent complications were urinary tract infection (15.4%), pneumonia (9.0%), and constipation (6.8%).

In S*tudy I,* we examined the predictive values, sensitivity, and specificity of medical complications among patients admitted to specialized stroke units and registered in the Danish National Indicator Project and the Danish National Registry of Patients between January 2003 and December 2006 (n= 8,024). We retrieved and reviewed medical records from a random sample of patients (n = 589, 7.3%) using a standardized form. We found moderate to high predictive values for medical complication diagnoses among patients with stroke in the two population-based registries. However, the sensitivity varied substantially between the two registries, with the stroke registry

having a much higher sensitivity compared to the hospital discharge registry. The specificity of the diagnoses was high in both registries. We conclude that these findings indicate that data from the Danish National Indicator Project may be useful for studying medical complications in patients with stroke, particularly for analytical studies.

In *Study II,* we identified all patients with acute stroke who had been admitted and discharged between January 2003 and December 2008 (n=11,757). We found that patients who received recommended processes of care in the acute phase of stroke had a substantially lower risk of medical complications. The association between the number of processes of care received and medical complications appeared to follow a dose-response pattern. The lowest risk of complications was found among patients who received all relevant processes of care compared to patients who did not receive any of the processes. Of the individual processes of care, early mobilization was associated with the lowest risk of medical complications.

In *Study III,* we identified all patients with acute stroke who have been admitted and discharged between January 2003 and December 2009 (n=13,721). Follow-up started at the day at admission. We found that patients hospitalized with medical complications had significantly longer length of stay values than did patients without complications. In-hospital complications were also in particular for pneumonia associated with an increased mortality.

We conclude that the DNIP together with the other data sources used in this thesis may be useful for studying medical complications among patients with stroke. Patients who received a higher quality of stroke care during the early phase of stroke had a substantially lower risk of medical complications than those who did not. Medical complications were associated with a significantly longer length of stay and in particular for pneumonia also with an increased mortality.

DANISH SUMMARY

Inden for de seneste år er opmærksomheden omkring behandling af patienter med blodprop eller blødning i hjernen (apopleksi) øget. Apopleksi er en af de hyppigste dødsårsager og den vigtigste årsag til invaliditet i den vestlige verden. Medicinske komplikationer i forbindelse med indlæggelse for apopleksi er et alvorligt klinisk problem, da patienter med apopleksi har en stor risiko for at udvikle én eller flere medicinske komplikationer som lungebetændelse, urinvejsinfektion, faldtraumer, liggesår, venetrombose (blodprop i ben eller lunger) samt alvorlig obstipation sekundært til apopleksien. Der er imidlertid kun sparsom viden om, hvilke konsekvenser alvorlige medicinske komplikationer har for patienter indlagt med apopleksi, men tidligere studier har vist, at komplikationer muligvis kan forsinke/hindre optimal rehabilitering, øge indlæggelsestiden og være direkte årsag til død. De fleste eksisterende studier er dog små og ikke entydige.

Denne afhandling er baseret på et valideringsstudie og to follow-up studier udført i det tidligere Hovedstadens Sygehusfællesskab (H:S) og Århus Amt. Studierne bygger på data fra, Det Nationale Indikatorprojekt (NIP), Det Centrale Personregister, Landspatientregistret (LPR) og patientjournaler. Formålene med studierne var at undersøge (1) validiteten af registreringen af medicinske komplikationer hos patienter med apopleksi i henholdsvis (a) NIP-apopleksi databasen og (b) LPR med henblik på at afdække anvendeligheden af eksisterende data til brug for klinisk epidemiologiske studier, (2) sammenhængen mellem kvaliteten af akut behandling og pleje og risikoen for medicinske komplikationer opstået under indlæggelse og (3) sammenhængen mellem medicinske komplikationer opstået under indlæggelse og (a) indlæggelsesvarigheden og (b) 30 dages og 1-års dødeligheden.

I løbet af hele studieperioden (*studie III),* hvor i alt 13.721 patienter blev inkluderet, pådrog hver fjerde patient indlagt med akut apopleksi (25.2%, n=3.453) sig mindst én komplikation under indlæggelsen. De hyppigste komplikationer var urinvejsinfektion (15.4%), lungebetændelse (9.0%) og obstipation (6.8%).

Studie I blev gennemført som et valideringsstudie baseret på en stikprøve (n = 589, 7.3%) fra NIP-apopleksi databasen af alle konsekutivt registrerede patientforløb fra specialiserede apopleksiafsnit i det tidligere H:S og Århus Amt. Studiet omfattede patienter indlagt og udskrevet i perioden januar 2003 – december 2006 (n = 8.024). Vi foretog en standardiseret gennemgang af journalerne. De indsamlede oplysninger om tilstedeværelse af komplikationer i journalen blev herefter sammenlignet med de registrerede data vedrørende komplikationerne i den kliniske database, NIP-apopleksi databasen og i LPR. Herefter blev sensitivitet, specificitet, den positive og negative prædiktive værdi beregnet for henholdsvis komplikationsregistreringen i den kliniske database og LPR. Vi fandt moderate til høje prædiktive værdier for de medicinske komplikationsdiagnoser blandt patienter med apopleksi i de to populationsbaserede registre. Sensitiviteten varierede i midlertidig i betydelig grad mellem de to registre. NIP-apopleksi databasen havde en noget højere sensitivitet sammenlignet med LPR. Specificiteten af diagnoserne var høj i begge registre. Resultaterne dokumenterer, at den danske database NIP-apopleksi har en tilfredsstillende datakvalitet vedrørende registreringen af medicinske komplikationer. Databasen kan derfor være en værdifuld informationskilde i udforskningen af komplikationer hos patienter med apopleksi.

I Studie II inkluderede vi alle konsekutivt registrerede patienter i NIP- apopleksi fra afdelinger fra det tidligere H:S og Århus Amt i perioden januar 2003 – december 2008 (n=11.757). Vi fandt, at højere kvalitet af behandling og pleje i den akutte fase hos patienter, som indlægges med apopleksi, er associeret med en betydelig lavere risiko for at pådrage sig en medicinsk komplikation under indlæggelsen. Der var en invers dosis-respons sammenhæng mellem antallet af opfyldte procesindikatorer og risikoen for at pådrage sig en komplikation under indlæggelsen selv efter at der er taget højde for forskelle i patientsammensætningen mellem patienter, som henholdsvis får og ikke får den anbefalede behandling og pleje. Den laveste risiko blev fundet blandt de patienter, som fik opfyldt alle de procesindikatorer, der var vurderet relevant sammenlignet med de patienter, som ikke fik opfyldt nogen procesindikatorer. Blandt de specifikke procesindikatorer var tidlig iværksat mobilisering (indenfor 24 timer efter indlæggelsen) associeret med den laveste risiko.

I *Studie III* inkluderede vi alle konsekutivt registrerede i NIP- apopleksi fra afdelinger fra det tidligere H:S og Århus Amt i perioden januar 2003 – december 2009 (n=13.721). Follow-up startede på indlæggelsesdagen. Vi fandt, at indlæggelseslængden var signifikant længere hos patienter, der havde pådraget sig en komplikation under indlæggelsen sammenlignet med dem, der ikke oplevede nogen komplikationer under indlæggelsen. Forekomst af medicinske komplikationer, især lungebetændelse, var også forbundet med en øget dødelighed.

Sammenfattende viser de tre studier, at den landsækkende kliniske database NIP-apopleksi er en værdifuld kilde til undersøgelse af årsager til komplikationer hos patienter indlagt med apopleksi samt konsekvenserne af komplikationerne, når den kobles med andre datakilder anvendt i denne afhandling. Resultaterne viser, at højere kvalitet af den akutte behandling af patienter med apopleksi er forbundet med en betydelig lavere risiko for at pådrage sig medicinske komplikationer under indlæggelsen, og at forekomst af medicinske komplikationer under indlæggelsen med akut apopleksi er forbundet med en signifikant længere indlæggelsesvarighed, og især for lungebetændelse, også forbundet med en øget dødelighed.

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APPENDIX

Appendix I: Standardized form for review of medical records

Appendix II: Definitions of the medical complications

Appendix III: Charlson Comorbidity Index

Appendix IV: Study I

Appendix V: Study II

Appendix VI: Study III

Standardized form for review of medical records

Valideringsskema til journalgennemgang af medicinske komplikationer

Patientens ID.nr. i NIP	|___|___|___|___|___|___|
Patientens cpr.nr.:	|___|___|___|___|___|___|___|___|___|___|___|
Fornavn(e):	
Efternavn:	

Akut indlagt

\|___\|___\|___\|___\|___\|___\| \|___\|___\|___\|___\|

d d m m å å   t t m m

\|___\|___\|___\|___\| \|___\|___\|___\|

Sygehuskode   Afdelingskode

Apopleksiafsnit: □ Ja (1) □ Nej (2) □ Uoplyst (9)

Overflyttet til anden afdeling

Dato for evt. overflytning: \|___\|___\|___\|___\|___\|___\|

d d m m å å

Overflyttet til: \|___\|___\|___\|___\| \|___\|___\|___\|

Sygehuskode Afdelingskode

Apopleksiafsnit: □ Ja (1) □ Nej (2) □ Uoplyst (9)

Komplikationer under indlæggelsen

□ Ja (1): Undersøgelse udført svar positivt

□ Nej(2): Undersøgelse udført: svar negativt

□ Nej(3): Undersøgelse ej udført / ikke relevant

□ uoplyst (9): Undersøgelse udført – svar ej dokumenteret i journalen

Pneumoni

Kliniske oplysninger

Feber (> 37,5): □ Ja (1) □ Nej (2) □ Nej(3) □ uoplyst(9)

Hoste: □ Ja (1) □ Nej (2) □ Nej (3) □ uoplyst (9)

Åndenød: □ Ja (1) □ Nej (2) □ Nej (3) □ uoplyst (9)

Smerter i brystet: □ Ja (1) □ Nej (2) □ Nej (3) □ uoplyst (9)

Tiltagende eller gulligt opspyt: □ Ja (1) □ Nej (2) □ Nej (3) □ uoplyst (9)

Stetoskopiske rallelyde svarende til det sted hvor røntgenbilledet viste pneumoni:
□ Ja (1) □ Nej (2) □ Nej (3) □ uoplyst (9)

Fund af bakterier i patientens blod: □ Ja (1) □ Nej (2) □ Nej (3) □ uoplyst (9)

Tydeligt forhøjede infektionstal i blodprøverne:
□ Ja (1) □ Nej (2) □ Nej (3) □ uoplyst (9)

Diagnostisk baggrund

Påvist ved røntgen af lungerne: ☐ Ja (1) ☐ Nej (2) ☐ Nej (3) ☐ uoplyst (9)

Mindst ét klinisk tegn på pneumoni til stede: ☐ Ja (1) ☐ Nej (2)

Diagnosen er dokumenteret i patientjournalen ved røntgen + mindst ét klinisk tegn på pneumoni til stede: ☐ Ja (1) ☐ Nej (2)

Nedenstående oplysning anvendes ikke ved den primære analyse af validiteten

Diagnosen er dokumenteret i patientjournalen alene ved ét eller flere kliniske tegn på pneumoni: ☐ Ja (1) ☐ Nej (2)

Urinvejsinfektion

Kliniske oplysninger

Hyppige smertefulde vandladninger: Ja (1) ☐ Nej (2) ☐ Nej (3) ☐ uoplyst (9)

Smerter over symfysen ☐ Ja (1) ☐ Nej (2) ☐ Nej (3) ☐ uoplyst (9)

Hyppig vandladning: ☐ Ja (1) ☐ Nej (2) ☐ Nej (3) ☐ uoplyst (9)

Feber: ☐ Ja (1) ☐ Nej (2) ☐ Nej (3) ☐ uoplyst (9)

Ildelugtende urin: ☐ Ja (1) ☐ Nej (2) ☐ Nej (3) ☐ uoplyst (9)

Diagnostisk baggrund

Dyrkning og resistensundersøgelse - D+R positiv med signifikant bakteriuri (>10^5/ml):
☐ Ja (1) ☐ Nej (2) ☐ Nej (3) ☐ uoplyst (9)

Mindst ét klinisk tegn på urinvejsinfektion til stede: ☐ Ja (1) ☐ Nej (2)

Diagnosen er dokumenteret i patientjournalen: ☐ Ja (1) ☐ Nej (2)

Decubitus

Kliniske oplysninger

Symptomer beskrevet i form af én de følgende 4 gradinddelinger:

<u>Grad 1</u>

Rødme af huden: ☐ Ja (1) ☐ Nej (2) ☐ Nej (3) ☐ uoplyst (9)

Huden er intakt: ☐ Ja (1) ☐ Nej (2) ☐ Nej (3) ☐ uoplyst (9)

Rødmen forsvinder ikke ved fingertryk: ☐ Ja (1) ☐ Nej (2) ☐ Nej (3) ☐ uoplyst (9)

Smerter ☐ Ja (1) ☐ Nej (2) ☐ Nej (3) ☐ uoplyst (9)

Grad 1 kendetegn dokumenteret: ☐ Ja (1) ☐ Nej (2) ☐ Nej (3) ☐ uoplyst (9)

<u>Grad 2</u>

Vabeldannelse: ☐ Ja (1) ☐ Nej (2) ☐ Nej (3) ☐ uoplyst (9)

Overfladiske sår: ☐ Ja (1) ☐ Nej (2) ☐ Nej (3) ☐ uoplyst (9)

Smerter: ☐ Ja (1) ☐ Nej (2) ☐ Nej (3) ☐ uoplyst (9)

Grad 2 kendetegn dokumenteret: ☐ Ja (1) ☐ Nej (2) ☐ Nej (3) ☐ uoplyst (9)

<u>Grad 3</u>

Såret gennem dermis
og ind i det subkutane væv: ☐ Ja (1) ☐ Nej (2) ☐ Nej (3) ☐ uoplyst (9)

Nekroser: ☐ Ja (1) ☐ Nej (2) ☐ Nej (3) ☐ uoplyst (9)

Underminering: ☐ Ja (1) ☐ Nej (2) ☐ Nej (3) ☐ uoplyst (9)

Fistler i såret: ☐ Ja (1) ☐ Nej (2) ☐ Nej (3) ☐ uoplyst (9)

Grad 3 kendetegn dokumenteret: ☐ Ja (1) ☐ Nej (2) ☐ Nej (3) ☐ uoplyst (9)

<u>Grad 4</u>

Såret brudt gennem fascie, ned i muskelvæv
og evt. knogle og led: ☐ Ja (1) ☐ Nej (2) ☐ Nej (3) ☐ uoplyst (9)

Såret inficeret: ☐ Ja (1) ☐ Nej (2) ☐ Nej (3) ☐ uoplyst (9)

Smerter: ☐ Ja (1) ☐ Nej (2) ☐ Nej (3) ☐ uoplyst (9)

Grad 4 kendetegn dokumenteret: ☐ Ja (1) ☐ Nej (2) ☐ Nej (3) **☐ uoplyst (9)**

Diagnosen er dokumenteret i patientjournalen: ☐ Ja (1) ☐ Nej (2)

Faldtraume

Kliniske oplysninger

Hændelsen utilsigtet: ☐ Ja (1) ☐ Nej (2) ☐ Nej (3) ☐ uoplyst (9)

Kommet til at ligge på et lavere niveau: ☐ Ja (1) ☐ Nej (2) ☐ Nej (3) ☐ uoplyst (9)

Mindst én dags sengeleje(følge af traumet): ☐ Ja (1) ☐ Nej (2) ☐ Nej (3) ☐ uoplyst (9)

Diagnosen er dokumenteret i patientjournalen: ☐ Ja (1) ☐ Nej (2) ☐ uoplyst (9)

Dyb venetrombose

Kliniske oplysninger

Smerter i ekstremitet: □ Ja (1) □ Nej (2) □ Nej (3) □ uoplyst (9)

Rødme af ekstremitet: □ Ja (1) □ Nej (2) □ Nej (3) □ uoplyst (9)

Hævelse af ekstremitet: □ Ja (1) □ Nej (2) □ Nej (3) □ uoplyst (9)

Diagnostisk baggrund

Flebografi forenelig med DVT: □ Ja (1) □ Nej (2) □ Nej (3) □ uoplyst (9)

Dopplerultralyd til påvisning af proksimale tromber forenelig med DVT:
□ Ja (1) □ Nej (2) □ Nej (3) □ uoplyst (9)

Diagnosen er dokumenteret i patientjournalen: □ Ja (1) □ Nej (2)

Lungeemboli (LE)

Kliniske oplysninger

Dyspnøe (akut åndenød): □ Ja (1) □ Nej (2) □ Nej (3) □ uoplyst (9)

Tachypnøe: □ Ja (1) □ Nej (2) □ Nej (3) □ uoplyst (9)

Hoste: □ Ja (1) □ Nej (2) □ Nej (3) □ uoplyst (9)

Brystsmerter: □ Ja (1) □ Nej (2) □ Nej (3) □ uoplyst (9)

Mindst ét klinisk tegn på LE til stede: □ Ja (1) □ Nej (2)

Diagnostisk baggrund

Perfusions ventilations(P/V) lungescintigrafi forenelig med LE:
□ Ja (1) □ Nej (2) □ Nej (3) □ uoplyst (9)

CT– angio forenelig med LE: □ Ja (1) □ Nej (2) □Nej (3) □ uoplyst (9)

Elektrokardiogram (EKG) forenelig med LE: □ Ja (1) □ Nej (2) □ Nej (3) □ uoplyst (9)

D-dimer forhøjet: □ Ja (1) □ Nej (2) □Nej (3) □ uoplyst (9)

A-punktur – resultat = hyperventilation: □ Ja (1) □ Nej (2) □Nej (3) □ uoplyst (9)

Sandsynlige differentialdiagnoser: □ Ja (1) □ Nej (2) □Nej (3) □ uoplyst (9)

Diagnosen er dokumenteret i patientjournalen ved P/V eller CT-angio:
□ Ja (1) □ Nej (2) □

Diagnosen er dokumenteret ved: påvist DVT + kliniske symptomer forenelige med LE:
□ Ja (1) □ Nej (2)

Diagnosen er dokumenteret ved EKG + kliniske symptomer på LE + ingen sandsynlige differentialdiagnoser: Ja (1) □ Nej (2)

Obstipation

Kliniske oplysninger/kriterier:

Mindre end tre afføringer om ugen: □ Ja (1) □ Nej (2) □ Nej (3) □ uoplyst (9)

Afføringen beskrives som hård: □ Ja (1) □ Nej (2) □ Nej (3) □ uoplyst (9)

Følelsen af ikke at være færdig: □ Ja (1) □ Nej (2) □ Nej (3) □ uoplyst (9)

Smerter ved defækation: □ Ja (1) □ Nej (2) □ Nej (3) □ uoplyst (9)

Anstrengelse ved defækation: □ Ja (1) □ Nej (2) □ Nej (3) □ uoplyst (9)

Mindst to af ovenstående kriterier opfyldt: □ Ja (1) □ Nej (2)

Diagnostisk baggrund

Obstipationen har nødvendiggjort oliefosfatklysma:

□ Ja (1) □ Nej (2) □ Nej (3) □ uoplyst (9)

Diagnosen er dokumenteret i patientjournalen: □ Ja (1) □ Nej (2)

Appendix II

Definitions of the medical complications

Medical complication	Definition
Pneumonia	Description of clinical indications or positive chest radiograph
Urinary tract infection	Clinical symptoms of urinary infection combined with a positive culture and resistance examination (D+R positive with significant bacteriuria (>10^5/ml).
Pressure ulcer	Any skin break or necrosis documented in the medical record as symptoms resulting from pressure.
Falls after stroke	Any documented fall regardless of cause. It should be documented that the accident was inadvertent, and that the patient inadvertently fell down; i.e., with or without bed rest.
Venous thromboembolism	Either having clinical indication(s) of deep vein thrombosis supported by objective examination, or clinical indication(s) of pulmonary embolism supported by objective examination.
Constipation	Clinical symptoms combined with requirement for oil phosphate clysma (enemas).

Appendix III

Charlson Comorbidity Index

ICD-8 and ICD-10, and scoring for 19 disease categories used to calculate the Charlson Comorbidity Index.

Disease category	ICD-8	ICD-10	Score
Myocardial infarction	410	I21-I23	1
Congestive heart failure	427.09; 427.10; 427.11; 427.19; 428.99; 782.49	I50; I11.0; I13.0; I13.2	1
Peripheral vascular disease	440; 441; 442; 443; 444; 445	I70- I74; I77	1
Cerebrovascular disease	430-438	I60-I69; G45; G46	1
Dementia	290.09-290.19; 293.09	F00-F03; F05.1; G30	1
Chronic pulmonary disease	490-493; 515-518	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2-J98.3	1
Connective tissue disease	712; 716; 734; 446; 135.99	M05; M06; M08; M09; M30-M36; D86	1
Ulcer disease	530.91; 530.98; 531-534	K22.1; K25-K28	1
Mild liver disease	571; 573.01; 573.04	B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0	1
Diabetes	249.00; 249.06; 249.07; 249.09; 250.00; 250.06; 250.07; 250.09	E10.0; E10.1; E10.9; E11.0; E11.1; E11.9	1
Hemiplegia	344	G81; G82	2
Moderate to severe renal disease	403; 404; 580-584; 590.09; 593.19; 753.10-753.19; 792	I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61	2
Diabetes with end organ damage	249.01-249.05; 249.08; 250.01-250.05; 250.08	E10.2-E10.8; E11.2-E11.8	2
Any tumor	140-194	C00-C75	2
Leukemia	204-207	C91-C95	2
Lymphoma	200-203; 275.59	C81-C85; C88; C90; C96	2
Moderate to severe liver disease	070.00; 070.02; 070:04; 070.06; 070.08; 573.00; 456.00-456.09	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85	3
Metastatic solid tumor	195-199	C76-C80	6
AIDS	079.83	B21-B24	6

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ORIGINAL RESEARCH

Medical complications in patients with stroke: data validity in a stroke registry and a hospital discharge registry

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Background: Stroke patients frequently experience medical complications; yet, data on incidence, causes, and consequences are sparse.
Objective: To examine the data validity of medical complications among patients with stroke in a population-based clinical registry and a hospital discharge registry.
Methods: We examined the predictive values, sensitivity and specificity of medical complications among patients admitted to specialized stroke units and registered in the Danish National Indicator Project (DNIP) and the Danish National Registry of Patients (NRP) between January 2003 and December 2006 (n = 8,024). We retrieved and reviewed medical records from a random sample of patients (n = 589, 7.3%).
Results: We found substantial variation in the data quality of stroke-related medical complication diagnoses both within the specific complications and between the registries. The positive predictive values ranged from 39.0%–87.1% in the DNIP, and from 0.0%–92.9% in the NRP. The negative predictive values ranged from 71.6%–98.9% in the DNIP and from 63.3% to 97.4% in the NRP. In both registries the specificity of the diagnoses was high. The sensitivity ranged from 23.5% (95% confidence interval [CI]: 14.9–35.4) for falls to 62.9% (95% CI: 54.9–70.4) for urinary infection in the DNIP, and from 0.0 (95% CI: 0.0–4.99) for falls to 18.1% (95% CI: 2.3–51.8) for pressure ulcer in the NRP.
Conclusion: The DNIP may be useful for studying medical complications among patients with stroke.
Keywords: stroke, medical complications, data validity, clinical database

Introduction

Stroke patients frequently experience medical complications such as pneumonia, urinary infection, pressure ulcer, falls, venous thromboembolism, and severe constipation. These complications may hinder optimum rehabilitation and have been associated with increased mortality.[1–6] However, the available data on incidence, causes, and consequences of serious medical complications are sparse and inconclusive.[1–5]

Large-scale population-based studies, reflecting real-life conditions in modern stroke care, are much needed. Primary data collection is often time-consuming and costly; consequently, it is often only done on a smaller scale. Furthermore, there is a likelihood of bias due to recall, nonresponse, and effects on the diagnostic process as a result of the research question.[6–8] Clinical and administrative registries are possible alternatives to primary data collection, they have the advantage of readily available data and often contain complete registration of information on people in the target population. Registries are generally valuable tools for answering clinical, administrative, and research questions and may also be useful for studying medical complications in patients with stroke; however, documented reasonable data validity is a prerequisite for using such data sources.

To our knowledge, information on the validity of registry data on medical complications among stroke patients has not been reported previously. Therefore, we examined the data validity of medical complications among stroke patients in two population-based Danish registries: the Danish National Indicator Project (DNIP) and the Danish National Registry of Patients (NRP).

Methods

Data sources

The Danish healthcare system provides tax-supported health care to the country's 5.5 million residents, all of whom have free access to hospital care and general practitioners. Patients with acute medical conditions, including stroke, are exclusively admitted to public hospitals. The entire population is covered by a large number of administrative and medical registries, which are used for monitoring and regulating all central aspects of the public sector including the health care system. Through the use of a civil registry number, which is unique to every Danish citizen and encodes sex and date of birth, unambiguous linkages between the population-based registers can be made.[9]

The Danish National Indicator Project (DNIP)

In 2000, the DNIP was established as a nationwide initiative to monitor and improve the quality of treatment and care provided by the Danish health care system for specific diseases, including stroke. The project develops evidence-based quality criteria related to the structure, process, and outcome of health care and monitors the fulfillment of these criteria. Project participation is mandatory for all Danish hospitals, relevant clinical departments, and units treating patients with stroke.[10] Upon hospital admission, data on care and patient characteristics (eg, age, sex, marital status, housing, Scandinavian Stroke Scale score, history of stroke or myocardial infarction, previous and/or current atrial fibrillation, hypertension, diabetes mellitus or intermittent claudication, smoking habits, and alcohol intake) are collected for all patients admitted with stroke. Detailed written instructions are available to the staff to ensure the validity of the data collected and completeness of patient registration in the DNIP. After hospital discharge the data are entered into a central database. A structured audit process is carried out regularly (every year) on a national, regional, and local basis to assess critically the quality of the dataset and results. After the audit process is completed the data are released publicly, including comments on the results from the audit groups. To ensure completeness of patient registration in DNIP, its enrollees are compared with local hospital discharge registries.[10]

The Danish National Registry of Patients (NRP)

The NRP is an administrative nationwide public registry that covers all discharges from somatic hospitals in Denmark since January 1, 1977. The data include the civil registry number, which is unique to every Danish citizen, the dates of admission and discharge, the surgical procedure(s) performed, and up to 20 diagnoses for every discharge classified, since 1994, according to the Danish version of the International Classification of Diseases, 10th edition (ICD-10). All discharge diagnoses are assigned by the physician who discharges the patient. Reporting of all hospital contacts to the NRP is mandatory by law. Data reported to the NRP are also used for classifying the patients in relation to Diagnosis-related groups (DRG), which determines the financial compensation given to the hospital for treating the individual patients.[11]

Study population

We identified all admissions for acute stroke, from 10 specialized stroke units in the former Copenhagen Hospital Corporation and Aarhus County, registered in the DNIP from January 13, 2003 to December 31, 2006. All patients ($\geq$18 years) admitted to Danish hospitals with stroke, as defined by WHO criteria, ie, an acute disturbance of focal or global cerebral function with symptoms lasting more than 24 hours or leading to death of presumed vascular origin, are eligible for inclusion in the DNIP database. This includes patients with intracerebral hemorrhage and ischemic stroke (ICD-10: I63, infarction; I61, hemorrhage; and I64, unspecified). Patients with subarachnoidal 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 computed tomography (CT) or magnetic resonance imaging (MRI) scans are also excluded.

Although some patients had multiple events, we included only the first stroke event registered in the DNIP during the study period. Furthermore, only patients with a valid civil registry number (a unique personal identification number issued to all Danish citizens that allows unambiguous linkage between public registries) were included in the study. In total, we identified 8,024 (99.5%) admissions in the registry which were eligible for inclusion in our study population.

Medical complications in the DNIP

During hospital admission, detailed data on each patient are prospectively registered using a standardized form. The data includes the presence (and if so, date of diagnosis) or absence of the following seven medical complications: pneumonia, urinary infection, pressure ulcer, falls, deep venous thrombosis (DVT), pulmonary embolism (PE), and constipation. Only complications that occurred after hospital admission are registered.

Medical complications in the NRP

Information on medical complications during the hospital admission was obtained through linkage to the NRP. We retrieved data on the following ICD-10 discharge diagnoses: pneumonia (DJ12–DJ18), urinary infection (DN30.0, DN30.8, DN30.9, and DN10), pressure ulcer (DL899), falls (DR297 and EUHE), DVT (DI82.9, DI82.9A-E), PE (DI26), and constipation (DK590). Both primary diagnoses, the condition, which is the principal reason for the hospital admission, and secondary diagnoses, all other clinically relevant diagnoses, including any significant complications and symptoms that appear during the admission, were identified from the registry.

Medical record review

We aimed to retrieve and review medical records from a random sample of approximately 5% of patients in the defined study population (n = 417). A computer-generated 5% random sample was obtained from the entire study population, stratified according to the 10 stroke units serving the study population. Additionally, we retrieved and reviewed 25 medical records for each of the seven types of complications registered in the DNIP. The 25 extra medical records were selected randomly among all patients registered with medical complications in the DNIP. The later records were added to ensure a reasonable statistical precision of the estimated positive predictive value for relatively rare complications. In total, 589 records were retrieved and reviewed.

All medical records were retrieved and reviewed by a single reviewer (AI) using a standardized form. The form was developed and tested in close collaboration with 2 consultants in neurology and clinical epidemiology (GA, SPJ). The criteria used to define the presence of a complication were in accordance with existing international defined criteria or, if such criteria were not available, defined *a priori* by consensus among the authors.

The diagnostic criteria are presented in Table 1. All cases with uncertain diagnosis, based on the available information, were discussed with the consultants. The review was based on all available information in the medical records including written radiology reports, results from laboratory tests, and the nurse records. The actual brain imaging films were not re-interpreted. The study was approved by The Danish Data Protection Agency (J.no. 2007-41-0563) and The National Board of Health (J.no. 7-604-04-2/26/EHE).

Statistical analysis

The positive and negative predictive values of the registered complications in the DNIP and the NRP were assessed using the review of the medical records as the gold standard. Positive predictive values of the complications in the registries were computed as proportions with the number of patients with a verified complication, after review of medical records using the diagnostic criteria in Table 1, as the numerator and the total number of patients registered in the DNIP/NRP with this specific complication as the denominator. Negative predictive values of the complications in the registries were computed as proportions with the number of patients verified to not have the specific complication, after review of medical records using the diagnostic criteria in Table 1, as the numerator and the total number of patients registered in the DNIP/NRP without this specific complication as the denominator. We computed the sensitivity of the complications as the proportion of patients with a verified complication registered in the DNIP/NRP divided by the total number of patients in our random sample with a complication in the medical record. Specificity of the complications was similarly defined as the number of patients without any verified complication registered in the DNIP/NRP divided by the total number of patients in our random sample without a complication in the medical record.

Positive and negative predictive values, the sensitivity, and the specificity were calculated for all complications combined and for the specific complications (pneumonia, urinary infection, pressure ulcer, falls, DVT, PE, and constipation). Finally, we estimated the proportion of patients who had at least one symptom of a complication registered in their medical record among patients registered in the DNIP with the complication.

For all estimates, a 95% confidence interval (CI) was calculated. Data were analyzed using STATA® version 10.0 (StataCorp, College Station, TX, USA).

Table 1 The diagnostic criteria for the seven medical complications

Medical complication	Diagnostic test/objective examinations	Clinical indications in the medical record	Diagnosis is defined as correct if:
Pneumonia	X-ray examination showed an infiltration, Body temperature ≥37.5°C Microorganism isolated from blood culture, increased infection parameters	Cough Dyspnea Chest pain Rales coincident with the area of infiltration Increased sputum, purulent sputum	1) The patient's test radiographic examination showed an infiltration and at least one clinical indication 2) The sum of clinical indications was more than two.
Urinary infection	Culture and resistance examination (D + R) positive with significant bacteriuria ($>10^5$/ml)	Pain over the symphysis Frequent urge to urinate strangury Malodorous urine Fever	1) The infection has been shown in culture and resistance examination (D + R) positive with significant bacteriuria ($>10^5$ mL) and at least one clinical indication of urinary infection was present. 2) The urinary infection was shown by at least two clinical indications in the medical record.
Decubitus		**Graduation 1:** Skin: Red, intact. The red color does not disappear by finger pressure, the condition is painful. **Graduation 2:** Blisters or superficial wounds are seen, which rarely penetrate the dermis, the condition is painful. **Graduation 3:** The wound has penetrated the dermis and entered subcutaneous tissue; there may be necrosis, undermining, and possibly fistula in the wound. Muscle fascia will stop progression in depth. **Graduation 4:** The wound has broken through fascia down into muscle tissue and possibly bone and joint, is often infected. Generally there is no pain.	Decubitus was documented in the medical record as symptoms describing one of the graduations 1–4.
Falls after stroke		The accident was inadvertent, the patient inadvertently fell down, the patient has been confined to bed for at least one day because of the trauma.	It was documented that the accident was inadvertent, and that the patient fell down; ie, with or without bed rest. Both must be documented.
Deep vein thrombosis	Phlebography Doppler ultrasound	Leg pain Reddening Swelling in the area	DVT has been suggested by objective examination and there was at least one clinical indication of DVT.
Pulmonary embolism	Perfusion ventilation, pulmonary scintigraphy (P/V), CT-angio Echo diagram, Increased D-Dimer, A-puncture resulting in the form of hyperventilation	Dyspnea Tachypnea Chest pain Cough	1) Has been shown by P/V or computed tomography (CT) angiography 2) DVT has been shown, and at the same time there was one or several clinical indications 3) PE has been shown by echo diagram, increased D-dimer, and A-puncture, and one or several of the clinical indications were present and no probable differential diagnoses were shown.
Constipation	Oil phosphate clysma	Less than three feces a week Feces is described as inspissated A feeling of not having finished Defecation was painful/strenuous	1) The constipation has necessitated required oil phosphate clysma, and at least two of the clinical indications were present. 2) At least two clinical indications present have been fulfilled.

Results

Table 2 shows demographic and clinical characteristics of the 8,024 patients with acute stroke registered in the DNIP.

Table 3 shows the number of medical complications registered in the DNIP and NRP among the patients. During hospitalization, a total of 25.4 % (n = 2,039) of the patients were registered with at least one medical complication in the DNIP. The most common complications in the DNIP were urinary infection in 15.5% (n = 1,240), pneumonia in 8.4% (n = 670), and constipation in 6.8%, (n = 544) of the patients; whereas DVT and PE were only registered in 0.4% (n = 32 and n = 28, respectively) of the patients.

Table 2 Descriptive characteristics of the 8,024 patients with acute stroke[a] registered in the Danish National Indicator Project, 2003–2006

Characteristic	N (%)
Age (years):	
18–65	2308 (28.76)
65–80	3204 (39.93)
>80	2512 (31.31)
Sex:	
– Men	4009 (49.96)
– Women	4015 (50.04)
Marital status:	
– Living with partner, family, or friend	3511 (43.7)
– Living alone	4008 (49.95)
– Other	202 (2.5)
– Unknown	303 (3.8)
Housing:	
– Own home	6994 (87.2)
– Nursing home or other institution	576 (7.2)
– Other	138 (1.7)
– Unknown	316 (3.9)
Type of stroke:	
– Intracerebral hemorrhage	847 (10.6)
– Ischemic	6076 (75.7)
– Unspecified	1101 (13.5)
Scandinavian stroke scale:	
– Very severe, 0–14 points	654 (8.2)
– Severe, 15–29 points	696 (8.7)
– Moderate, 30–44 points	1271 (15.8)
– Mild, 45–58 points	3098 (38.6)
– Unknown	2305 (28.7)
Previous stroke:	
– Yes	1908 (23.8)
– No	5585 (69.6)
– Unknown	531 (6.6)
Previous myocardial infarction:	
– Yes	745 (9.3)
– No	6638 (82.7)
– Unknown	641 (8.0)
Atrial fibrillation[b]:	
– Yes	1454 (18.1)
– No	6050 (75.4)
– Unknown	520 (6.5)
Hypertension[b]:	
– Yes	3856 (48.1)
– No	3529 (44.0)
– Unknown	639 (7.9)
Diabetes mellitus[b]:	
– Yes	1237 (15.4)
– No	6276 (78.2)
– Unknown	511 (6.4)
Claudicatio intermittens[b]:	
– Yes	363 (4.5)
– No	6214 (77.4)
– Unknown	1447 (18.0)
Smoking habits (%):	
– Current	2875 (35.3)
– Former (Quit more than ½ yr previously)	1402 (17.5)
– Never	2183 (27.2)
– Unknown	1564 (19.5)
Alcohol intake (%)[c]:	
– ≤21/14 drinks/week	5853 (72.9)
– >21/14 drinks/week	671 (8.4)
– Unknown	1500 (18.7)
Rankin score (%):	
0–1	4739 (59.0)
2–3	1313 (16.4)
4–5	502 (6.3)
– Unknown (+ missing)	1470 (18.3)

Notes: [a]Patients are from the former Copenhagen Hospital Corporation and Aarhus County; [b]Known history or diagnosed during current admission; [c]Drinks per week for men and women, respectively.

Table 4 presents the positive and negative predictive values of all the reviewed medical complications in the DNIP and NRP. We found the overall positive predictive value for the medical complications registered in the DNIP was 71.7% (95% CI: 67.4–75.8) compared to 76.1% (95% CI: 75.9–84.6) in the NRP. The positive predictive values in the DNIP ranged from 39.0% (95% CI: 24.2–55.5) for pressure ulcer to 87.1% (95% CI: 78.0–93.4) for pneumonia. In the NRP, there was even more variation in the positive predictive values, which ranged from 0.0 % (95% CI: 0–97.5) for falls to 92.9% (95% CI: 66.1–99.8) for pneumonia. The overall negative predictive

Table 3 Proportions of medical complications registered in the Danish National Indicator Project (DNIP) and the National Registry of Patients for the 8,024 patients with acute stroke registered in the DNIP, 2003–2006

Medical complication	The Danish National Indicator Project	The National Registry of Patients
	N (%)	N (%)
Pneumonia		
– Yes	670 (8.4)	122 (1.5)
– No	6,637 (82.7)	7,902 (98.5)
– Unknown	717 (8.9)	–
Urinary infection		
– Yes	1,240 (15.5)	391 (4.9)
– No	6,070 (75.7)	7,633 (95.1)
– Unknown	714 (8.9)	–
Decubitus		
– Yes	110 (1.4)	20 (0.25)
– No	7,225 (90.0)	8,004 (99.75)
– Unknown	689 (8.6)	–
Falls after stroke		
– Yes	204 (2.5)	10 (0.12)
– No	7,082 (88.3)	8,014 (99.88)
– Unknown	738 (9.2)	–
Deep vein thrombosis		
– Yes	32 (0.40)	15 (0.2)
– No	7,323 (91.3)	8,009 (99.8)
– Unknown	669 (8.3)	–
Pulmonary embolism		
– Yes	28 (0.4)	24 (0.3)
– No	7,314 (91.2)	8,000 (99.7)
– Unknown	682 (8.5)	–
Constipation		
– Yes	544 (6.8)	57 (0.7)
– No	6,667 (83.1)	7,967 (99.3)
– Unknown	813 (10.1)	–

value registered in the DNIP was 91.3% (95% CI: 90.3–92.2). The negative predictive values in the DNIP ranged from 71.6% (95% CI: 67.2–75.7) for pneumonia to 98.9% (95% CI: 97.5–99.6) for pulmonary embolism. The overall negative predictive value for the medical complications registered in the NRP was 85.1% (95% CI: 83.9–86.1), the values ranged from 63.3% (95% CI: 59.2–67.3) for pneumonia to 97.4% (95% CI: 95.8–98.5) for pulmonary embolism.

Table 5 shows the sensitivity and specificity of the medical complications in the DNIP and NRP. The estimates are based on a 5% random sample of all patients with stroke registered in DNIP in the study period.

Sensitivity

The overall sensitivity of the seven medical complications in the DNIP and NRP was 40.9% (95% CI: 36.6–45.4) and 7.7% (95% CI: 5.6–10.3), respectively. The lowest sensitivity in both registries was found for falls (ie, 23.5% [95% CI: 14.9–35.4] in the DNIP and 0.0% [95% CI: 0.0–4.99] in the NRP). The highest sensitivity in the DNIP was for urinary infection, 62.9% (95% CI: 54.9–70.4); whereas, the highest in the NRP was for pressure ulcer, 18.1% (95% CI: 2.3–51.8).

Specificity

The overall specificity of the seven medical complications was 97.3% (95% CI: 96.7–97.8) in the DNIP and 99.5% (95% CI: 99.2–99.7) in the NPR. The specificity ranged from 93.4% (95% CI: 91.0–95.8) for urinary infection to 99.8% (95% CI: 98.9–100) for PE in the DNIP. In the NRP, the specificity ranged from 98.0% (95% CI: 96.1–99.1) for urinary infection to 100% (95% CI: 99.9–100) for PE. In a sub analysis (data not shown), we found that of the 130 complications

Table 4 Positive and negative predictive values for all the reviewed medical complications in the Danish National Indicator Project and the National Registry of Patients

Medical complication	The Danish National Indicator Project				The National Registry of Patients			
	Verified N/total N	Positive predictive value % (95% CI)	Total negative N/total N	Negative predictive value % (95% CI)	Verified N/total N	Positive predictive value % (95% CI)	Total negative N/total N	Negative predictive value % (95% CI)
Pneumonia	74/85	87.1 (78.0–93.4)	330/461	71.6 (67.2–75.7)	13/14	92.9 (66.1–99.8)	364/575	63.3 (59.2–67.3)
Urinary infection	122/149	81.9 (74.7–87.7)	340/399	85.2 (81.3–88.5)	30/39	76.9 (60.7–88.9)	390/550	70.9 (66.9–74.7)
Decubitus	16/41	39.0 (24.2–55.5)	498/506	98.4 (96.9–99.3)	4/8	50 (15.7– 84.3)	561/581	96.6 (94.7–97.9)
Falls after stroke	35/47	74.5 (59.7–86.1)	444/496	89.5 (86.5–92.1)	0/1	0.0 (0.0–97.5)	497/588	84.5 (81.3–87.4)
Deep vein thrombosis	20/28	71.4 (51.3–86.8)	521/524	99.4 (98.3–99.9)	7/8	87.5 (47.3–99.7)	564/581	97.1 (95.4–98.3)
Pulmonary embolism	17/26	65.4 (44.3–82.8)	520/526	98.9 (97.5–99.6)	10/11	90.9 (58.7–99.8)	563/578	97.4 (95.8–98.5)
Constipation	46/84	54.8 (43.5–65.7)	416/450	92.4 (89.6–94.7)	3/7	42.9 (9.9–81.6)	493/582	84.7 (81.5–87.5)
Overall	330/460	71.7 (67.4–75.8)	3069/3362	91.3 (90.3–92.2)	67/88	76.1 (75.9–84.6)	3432/4035	85.1 (83.9–86.1)

Abbreviation: CI, confidence interval.

registered in DNIP that were not verified during the review of the medical records, 57% (95% CI: 48.7–66.3) (n = 75) of these patients had a least one or more symptoms registered in their medical record which indicated the presence of a medical complication, but was not sufficient to fulfill the diagnostic criteria listed in Table 1.

Discussion

We found substantial diagnosis- and register-specific variation when validating the data quality of seven stroke-related medical complications registered in public Danish registries. The positive and negative predictive values were generally moderate to high for most complications in the two registries. In addition, the specificity of the medical complication diagnoses was high for all complications in the two registries. In contrast, major differences were found in the two registries for the sensitivity of the medical complication diagnoses. The sensitivity for all types of complications was moderate to low in the DNIP, whereas it was extremely low in the NRP.

Table 5 Sensitivity and specificity of the medical complications in the Danish National Indicator Project and the National Registry of Patients[a]

Medical complication	The Danish National Indicator Project				The National Registry of Patients			
	Verified positive/ total N	Sensitivity % (95% CI)	Verified negative/ total N	Specificity % (95% CI)	Verified positive/ total N	Sensitivity % (95% CI)	Verified negative/ total N	Specificity % (95% CI)
Pneumonia	51/182	28.0 (21.6–35.1)	330/339	97.3 (95.0–98.8)	12/201	6.0 (3.1–10.2)	362/363	99.7 (98.5–100)
Urinary infection	100/159	62.9 (54.9–70.4)	340/364	93.4 (90.3–95.7)	24/168	14.3 (9.4–20.5)	388/396	98.0 (96.1–99.1)
Decubitus	3/11	24.4 (6.02–61.0)	498/511	97.5 (95.7–98.6)	2/11	18.11 (2.3–51.8)	550/553	99.5 (98.4–99.9)
Falls after stroke	16/68	23.5 (14.9–35.4)	444/450	98.7 (97.1–99.5)	0/72	0 (0–4.99)	491/492	99.8 (98.9–100)
Deep vein thrombosis	2/5	40.0 (5.27–85.3)	521/525	99.2 (98.1–99.8)	1/6	16.7 (0.4–64.1)	561/561	100 (99.3–100)
Pulmonary embolism	0/6	–	520/521	99.8 (98.9–100)	0/8	–	556/556	100 (99.9–100)
Constipation	31/65	47.7 (35.1–60.5)	416/444	93.7 (91.0–95.8)	3/77	3.9 (0.8–11.0)	484/487	99.4 (98.2–99.9)
Overall	203/496	40.9 (36.6–45.4)	3069/3154	97.3 (96.7–97.8)	42/543	7.7 (5.6–10.3)	3392/3408	99.5 (99.2–99.7)

Notes: [a]Based on a 5% random sample of all patients registered in the study period.
Abbreviation: CI, confidence interval.

The strengths of our study included the population-based design, the access to medical records with detailed clinical data, and the standardized evaluation of the records including the use of well-defined diagnostic criteria developed in accordance with available existing literature and/or international consensus. The use of a single reviewer, who was not blinded for the diagnosis in DNIP, of the medical records was a potential methodological limitation as there exist a possibility of error in extracting information from the medical records. The use of retrospective review of medical records may also be a limitation as the collection and the quality of the data are not under control of the researcher (eg, the required information to make a valid conclusion about the presence of specific medical complications were always available in the medical records).

However, detailed diagnostic criteria and a standardized form were used to reduce any risk of bias in the data collection. Furthermore, all cases with uncertain diagnosis, based on the available information, were discussed with senior consultants. Although the number of reviewed medical records was relatively large compared to other validation studies based on detailed review of medical records, some of the complications (eg, deep venous thrombosis and pulmonary embolism) were rare with relatively few cases available for assessment. Consequently, the precision of the estimated predictive values, sensitivity, and specificity for these complications were only moderate. Finally, it is not known to what extent our findings can be extrapolated to other settings, where the prevalence of complications and the diagnostic strategy may be different.

We are unaware of other studies validating the quality of diagnoses of medical complications among patients with stroke in administrative and clinical registries. There may be different possible explanations for the low sensitivity we found in the NRP. However, the fact that there is no financial incentive for the stroke units to register medical complications in NRP due to the DRG system used in Denmark (ie, medical complications do not result in additional compensation to the hospital), is likely to be a major factor. Furthermore, registration of data to the NRP is done by physicians, whereas nurses are much more involved in the reporting of data to the DNIP. It is our impression that the nurses in general are much more aware of registration of medical complications, which may explain the higher sensitivity found in DNIP.

However, our finding of moderate to high positive predictive values in both registries are generally in accordance with the results from a number of validation studies concerning medical complications in different patient populations (eg, unselected internal medicine patients, pregnant women, patients from geriatric wards, general practice, or with a former cancer diagnosis).[12–22] The positive predictive values reported from these studies have ranged from 20.7% for pressure ulcer to 96.2% for pneumonia.[12–15,17–22] Only a few studies have previously reported the sensitivity and specificity of diagnoses of medical complications in registries. Quan et al examined diagnoses of complications in Canadian administrative hospital discharge data and found that the sensitivity ranged from 0% to 57.1% (higher than 50% for only two conditions). In contrast, specificity was generally high (range: 99.0%–100%).[16] These results are very consistent with our findings and also in line with findings from validation studies on other diagnoses not related to medical complications.[23,24] The implications of the often low sensitivity and high specificity of diagnoses in administrative and clinical registries depend on the research question and the design of the study.[8] A low sensitivity would result in misleading rates in a study determining incidence (eg, of medical complications among patients with stroke), whereas analytical studies examining associations would likely produce unbiased relative risk estimates due to the high specificity.[25] Thus, in analytical studies, a low specificity would be far more troublesome in most situations than a low sensitivity.[23] The fact that half of the complications not verified had a least one or several symptoms of the specific complications registered in the medical record supports this and indicates data on complications in the DNIP are valid, although the international criteria of the specific complication were not completely fulfilled.

Conclusion

In conclusion, we found moderate to high predictive values for medical complication diagnoses among patients with stroke in two population-based registries. However, the sensitivity varied substantially between the two registries with the stroke registry having a much higher sensitivity compared to the hospital discharge registry. The specificity of the diagnoses was high in both registries. These findings indicate that data from the DNIP may be useful for studying medical complications in patients with stroke, particularly for analytical studies.

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Study II

Processes of care and medical complications in patients with stroke

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ABSTRACT

Background and purpose: The relationship between processes of care and the risk of medical complications in patients with stroke remains unclear. We therefore examined the association in a population-based follow-up study.

Methods: We identified 11,757 patients admitted for stroke to stroke units in two Danish counties in 2003–2008. The examined processes of care included early admission to a stroke unit, early initiation of antiplatelet or oral anticoagulant therapy, early computed tomography/magnetic resonance imaging (CT/MRI) scan, and early assessment by a physiotherapist and an occupational therapist of nutritional risk and of swallowing function and early mobilization.

Results: Overall, 25.3% (*n* = 2,969) of the patients experienced one or more medical complications during hospitalization. The most common medical complications were urinary tract infection (15.5%), pneumonia (8.8%), and constipation (7.0%). We found indications of an inverse dose-response relationship between the number of processes of care that the patients received and the risk of medical complications. The lowest risk of complications was found among patients who received all relevant processes of care compared to patients who failed to receive any of the processes (i.e., adjusted odds ratios (OR) ranged from 0.42 ([95% confidence interval (CI): 0.24–0.74) for pressure ulcer to 0.64 (95% CI: 0.44–0.93) for pneumonia). Of the individual processes of care, early mobilization was associated with the lowest risk of complications.

Conclusions: Higher quality of acute stroke care was associated with a lower risk of medical complications.

Prevention and management of post stroke medical complications are essential aspects of stroke care, as patients with acute stroke are at high risk of medical complications, such as pneumonia, pressure ulcers and venous thromboembolism(VTE).[1,2] Previous studies have reported that up to 96% of all patients hospitalized for stroke experience medical or neurological complications during their hospitalization.[2–12] The reported risk estimates vary substantially; however, it is evident that medical complications are common. Although complications may hinder optimum rehabilitation and have been associated with increased mortality,[2-7,9-16] data regarding the causes of medical complications are sparse and inconclusive.[2,4,6,11,13]

Randomized controlled trials (RCT) have demonstrated the efficacy of some specific processes of care in relation to stroke outcomes, including admission to specialized stroke units and use of thrombolysis, antiplatelet drugs, and oral anticoagulants for selected patient groups.[17–19] However, the effectiveness of specific care processes in preventing medical complications remain uncertain. To fill this gap in knowledge, we examined the association between processes of care—as reflected by fulfillment of quality of care criteria for a range of specific processes—and the risk of medical complications in patients with acute stroke in a population-based follow-up study.

METHODS

We conducted this study using Danish medical registries. Since 1968, every Danish citizen has been assigned a unique ten-digit civil registration number, which is used in all Danish registries, enabling unambiguous linkage between them.[20] The Danish National Health Service provides tax-supported health care to all residents, including free access to hospital care and general practitioners. All acute medical conditions, including stroke, are exclusively treated at public hospitals in Denmark.[21]

Study population

Patients were identified from the Danish National Indicator Project (DNIP), a nationwide initiative to monitor and improve the quality of care for specific diseases including stroke.[22] Participation is mandatory for all Danish hospitals treating patients for stroke.

We identified all admissions for acute stroke to stroke units (n = 10) in the former Copenhagen Hospital Corporation and Aarhus County between 13 January 2003 and 31 December 2008. All patients (≥18 y old) who were admitted with stroke were eligible for inclusion in the DNIP. We only included the first stroke event registered in the study period and only patients with a valid civil registry number. In total, 11,757 admissions were available for analysis.

Processes of care

An expert panel including physicians, nurses, physiotherapists, and occupational therapists identified nine processes of care covering the acute phase of stroke.[22] A time frame was defined for each process to capture the timeliness of the processes (Table 1).

Using a registration form with detailed written instructions, data regarding processes of care were prospectively collected from the time of admission. Patients were classified as eligible or noneligible for the specific processes of care depending on whether the professionals treating the patient identified contraindications; e.g., severe dementia in a patient with ischemic stroke and atrial fibrillation precluding oral anticoagulant therapy or rapid spontaneous recovery of motoric symptoms, making early assessment by a physiotherapist and an occupational therapist irrelevant. In the written instructions, the criteria for deeming a patient ineligible for the care processes were specified.

Medical complications

During hospital admission, the following complications were registered: pneumonia, urinary tract infection, pressure ulcer, falls, deep venous thrombosis (DVT), pulmonary embolism (PE), and severe constipation. Only complications that developed after hospital admission were registered. The definitions (Table 2) of the medical complications were in general in accordance with definitions previously used in other studies.[2,4,9]

Patient characteristics

Data regarding the following characteristics were collected at the time of hospital admission: age, sex, marital status (living with partner, family, or friend or living alone), housing (own home, nursing home, or other institution), profession (employed, unemployed, or pensioner), Scandinavian Stroke Scale (SSS) score, Charlson comorbidity index (0, no comorbidity; 1–2, low comorbidity; ≥3, high comorbidity), previous stroke, previous and/or current atrial fibrillation, preadmission modified Rankin score, smoking habits (current, former (>1/2year), or never), and alcohol intake (≤21/14 or >21/14 drinks per week for men and women, respectively).

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

The preadmission modified Rankin score reflects the patients' functional ability prior to the stroke. The scale grades the patients from grade 0 (no symptoms) to grade 5 (severe disability) with a moderate inter-observer agreement.[24]

The Charlson comorbidity index score, which covers 19 major disease categories, was computed for each patient based on all discharge diagnoses recorded before the hospitalization for stroke.[25] Data were obtained from the National Registry of Patients, which contains data on all discharges from nonpsychiatric hospitals in Denmark since 1977.[26]

Length of hospital stay (LOS) was computed and defined as the time span from hospital admission to hospital discharge. The study was approved by The Danish Data Protection Agency (J.no.2007-41-0563).

Statistical analysis

First, we examined the association between the proportion of received processes of care and the individual medical complications. Because antiplatelet therapy and oral anticoagulant therapy are mutually exclusive, we combined these two processes (antiplatelet or anticoagulant therapy) in this analysis. The maximum number of processes of care received was therefore only eight in this case. Second, we examined the association between each process of care and the individual medical complications. Patients were only included in the analyses if they were considered eligible for the specific processes of care, and the LOS was >0. Logistic regression was used to obtain crude and adjusted odds ratios (OR). The latter were adjusted for all of the above-mentioned patient characteristics, and in the analyses of specific processes of care, were also mutually adjusted for the remaining processes of care. Age and SSS score were included as natural cubic splines. In all of the analyses, we corrected for clustering of patients by department. The Wald test was used to test for trends in the association between the proportion of received processes of care and the individual medical complications.

We used multiple imputation to impute missing values of the patient characteristics assuming that data was missing at random.[27,28] We imputed five datasets using the following variables: age, sex, marital status, housing, profession at admission, alcohol intake, smoking habits, atrial fibrillation, hypertension, SSS score, preadmission modified Rankin score, previous stroke, stroke subtype, calendar year, stroke unit identifier, and proportion of fulfilled quality of criteria. All analyses were performed both with and without the imputed data.

Finally, we stratified the analyses according to age, sex, and SSS score. STATA version 10.1 (StataCorp LP, College Station, TX, USA) was used to perform the analyses.

RESULTS

Nearly all of the patients (>95%) received early antiplatelet therapy, early examination with CT/MRI scan, and early assessment by a physiotherapist or an occupational therapist before discharge, although not necessarily before the defined time frame (data not shown).

The OR for these processes, as well as for early admission to a stroke unit (because only patients admitted to a stroke unit were included), therefore reflects the effect of early versus late intervention.

Table 3 shows patient characteristics as well as cumulative risk of medical complications and processes of care among the 11,757 patients. A total of 25.3% (*n* = 2,969) of the patients experienced at least one medical complication during their hospitalization. The most frequent complications were urinary tract infection (15.5%), pneumonia (8.8%), and constipation (7.0%). The overall 30-day mortality rate was 9.1%.

Figure 1 presents adjusted ORs for the individual medical complications according to the proportion of received processes of care. We found indications of an inverse dose-response relationship between the number of received processes and the risk of medical complications; the lowest complications rate was found among patients who received all relevant processes compared to patients who did not receive any of the processes (i.e., adjusted OR ranged from 0.42 (95% CI: 0.24–0.74) for pressure ulcer to 0.64 (95% CI: 0.44–0.93 for pneumonia). The test for trend was statistically significant for all medical complications except for VTE and constipation. The dose-response relationship was consistently found in all subgroups when stratifying by age, sex, and stroke severity (data not shown).

Table 4 shows adjusted ORs according to the specific processes of care. Six of the nine processes appeared to be associated with a lower risk for one or more medical complications (adjusted OR 0.43–0.97), although not all of the associations were statistically significant. Early CT/MRI scans and assessment by a physiotherapist or an occupational therapist was associated with an increased risk of any complication (adjusted OR 1.10–1.52).
Of the individual processes of care, early mobilization was associated with the lowest risk of medical complications (i.e., adjusted OR ranged from 0.43 (95% CI: 0.34–0.54) for pneumonia to 1.01 (95% CI: 0.57–1.78) for VTE). However, early initiation of oral anticoagulant therapy was also associated with a significantly reduced risk of pneumonia, VTE, and constipation; adjusted ORs were 0.64 (95% CI: 0.46–0.89), 0.17 (95% CI: 0.05–0.55), and 0.52 (95% CI: 0.33–0.81), respectively.

DISCUSSION

We found that higher quality of care, characterized by early intervention during the acute phase of stroke, was associated with a lower risk of medical complications during hospitalization. The association remained after adjusting for a wide range of possible confounding factors and appeared to follow a dose-response relationship in all of the examined subgroups.

The strengths of our study include the prospective, population-based design and the large number of patients included. As always in observational studies, possible unaccounted for and residual confounding is a concern. Several precautions were taken to minimize the impact of possible confounding, including control for a wide range of well-established prognostic factors (e.g., stroke severity), as well as clustering at the individual stroke units. Furthermore, only patients who were considered eligible for care by the staff were included in analyses of the individual processes of care, thereby minimizing the risk of confounding by indication. However, residual confounding by indication may remain in some of the associations that we studied, as indicated by the apparent increased risk of complications associated with some of the relevant processes of care received (e.g., patients with the worst prognosis, including patients who deteriorated during the first hours following hospitalization, are more likely to receive an early CT/MRI).
Thorough efforts are made to ensure the data validity in DNIP.[22] Regular audits are conducted which include validation of the completeness of patient registration against hospital discharge registries. Furthermore, we have examined the validity of the medical complications and found a high specificity (i.e., 97.3% c) and reasonable overall positive predictive value (i.e., 71.7 % [95% CI 67.4–75.8]).[29]

Despite differences among studies regarding selection of patients, duration of follow-up, definitions of complications, and types of complications, the risks of most of the individual medical complications in our study were in agreement with those found in other studies.[2,6,7,10,12,15] We did, however, find a lower risk of falls (2.5%) and constipation (7.0 %) than in most other studies, where reported risks of falls have ranged from 8.4% to 25%, [2,4,5,9,11] and risks of constipation ranged from 16% to 66%.[7,30] This difference may reflect that we only included patients treated in a stroke unit as the units are believed to be effective in preventing complications.[17,31,32]
Our finding of an association between processes of care and medical complications in patients with stroke is generally in accordance with the results of the few existing studies. The minor inconsistencies among the studies may stem from relatively small sample sizes, selection of study populations (e.g., most patients were not treated in stroke units), retrospective study designs, and differences between the examined processes of care and complications.[4,9,12] Furthermore, the validity of the data registered on medical complications is uncertain in the previous studies.[29]
Studies of medical complications following stroke are generally difficult to perform, because they require a systematic approach, as well as valid reporting in a sufficiently large population.[2,4,5,7,8,11]

In a Cochrane review (Kwan 2004), which included three RCTs and 12 nonrandomized studies, patient management with stroke care pathways was found to be associated with a lower risk of developing certain complications, such as urinary tract infections and readmissions. No significant differences in risk were found for other complications such as DVT, pressure scores, pneumonia, falls, and constipation; although the point estimates indicated that patient management with stroke care pathways might have a protective effect.[19] Our finding of an increased risk of falling when patients were mobilized early is in line with the findings of Czernuszenko et al.[33] Furthermore, implementation of evidence-based guidelines for nutrition, including early assessment of nutritional risk and early assessment of a physiotherapist or an occupational therapist, has previously been reported to be associated with a reduced risk of pneumonia and urinary tract infections among patients with stroke.[34]

Overall, the evidence supports the use of care pathways in acute stroke care [32] and an early multidisciplinary effort to ensure optimal care to prevent medical complications. Many questions remain about the specific processes responsible for this effect;[35] however, a key difference between stroke unit care and general wards seems to be earlier initiation of rehabilitation[17] and mobilization and careful monitoring of clinical parameters.[13,35,36]

Our finding of a reduced risk of medical complications following early mobilization is in accordance with the findings of a recent RCT , where early mobilization in the form of passive turning and mobilization during the acute phase of an ischemic stroke decreased the incidence of pneumonia.[38] The optimal timing of mobilization has so far been unclear, but mobilization within the first few days seems to be well tolerated and not harmful.[39] Our study verifies the importance of very early mobilization within the first postadmission day.

In conclusion, we found that high quality of care with early intervention in the acute phase of stroke with specific processes of care was associated with a substantially lower risk of medical complications in a large population-based follow-up study.

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TABLE 1. Definitions of processes of care.

Proces of care	Definition	Time frame
Admission to a specialized stroke unit.	Admission to a hospital department/unit that exclusively or primarily is dedicated to patients with stroke and which is characterized by multidisciplinary teams, a staff with a specific interest in stroke, involvement of relatives, and continuous education of the staff.	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.
Examination with CT/MRI scan.		First day of hospitalization.
Assessment by a physiotherapist/occupational therapist.	Formal bed-side assessment of the patient's need for rehabilitation.	Second day of hospitalization.

Assessment of nutritional risk.	Assessment following the recommendations of the European Society for Parenteral and Enteral Nutrition; i.e., calculation of a score that accounts for both the nutritional status and the stress induced by the stroke.	Second day of hospitalization.
Early assessment of swallowing function.	Assessment according to the Gugging Swallowing Screen.	First day of hospitalization.
Early mobilization.	Nurse or physio/occupational therapy team performing mobilization and out-of-bed (sitting, standing or walking) mobilization.	First day of hospitalization.

TABLE 2. Definitions of medical complications.

Medical complication	Definition
Pneumonia	Description of clinical indications or positive chest radiograph.
Urinary tract infection	Clinical symptoms of urinary infection combined with a positive culture and resistance examination (D+R positive with significant bacteriuria (>10^5/ml).
Pressure ulcer	Any skin break or necrosis documented in the medical record as symptoms resulting from pressure.
Falls after stroke	Any documented fall regardless of cause. It should be documented that the accident was inadvertent, and that the patient inadvertently fell down; i.e., with or without bed rest.
Venous tromboembolism (VTE)	Either having clinical indication(s) of deep vein thrombosis supported by objective examination, or clinical indication(s) of pulmonary embolism supported by objective examination.
Constipation	Clinical symptoms combined with requirement for oil phosphate clysma(enemas).

TABLE 3. Descriptive characteristics of 11,757 patients with acute stroke admitted to stroke units in Copenhagen and Aarhus areas between 2003-2008.

Characteristics	***N* (%)**
Age (y)	
18–65	3,295 (28.0)
>65–80	4,829 (41.1)
>80	3,633 (30.9)
Sex	
-Men	5,885 (50.1)
-Women	5,872 (49.9)
Marital status	
-Living with partner, family, or friend	5,185 (44.1)
-Living alone	5,914 (50.3)
-Other	309 (2.6)
-Unknown	349 (3.0)
Housing	
-Own home	10,351 (88.0)
-Nursing home or other institution	838 (7.1)
-Other	192 (1.6)
-Unknown	376 (3.2)
Profession at admission	
-Employed/unemployed	1,958 (16.7)
-Pensioner	8,577 (73.0)
-Other form of profession	167 (1.4)
-Unknown	1,055 (9.0)
Type of stroke	
-Intracerebral hemorrhage	1,326 (11.3)
-Ischemic	9,238 (78.6)
-Unspecified	1,244 (10.6)
Scandinavian Stroke Scale on admission	
-Very severe, 0–14 points	920 (7.8)
-Severe, 15–29 points	1,022 (8.7)
-Moderate, 30–44 points	1,821 (15.5)

-Mild, 45–58 points	4,548 (38.7)
-Unknown	3,446 (29.3)
Previous stroke	
-Yes	2,635 (22.4)
-No	8,483 (72.2)
-Unknown	639 (5.4)
Atrial fibrillation*	
-Yes	2,176 (18.5)
-No	8,970 (76.3)
-Unknown	611 (5.2)
Hypertension*	
-Yes	6,129 (52.1)
-No	4,884 (41.5)
-Unknown	744 (6.3)
Smoking habits	
-Current	4,218 (35.9)
-Former	2,224 (18.9)
-Never	3,203 (27.2)
-Unknown	2,112 (18.0)
Alcohol intake†	
-≤21/14 drinks/week	8,797 (74.8)
->21/14 drinks/week	1,020 (8.7)
-Unknown	1,940 (16.5)
Rankin score (before admission)	
-No/no significant symptoms 0–1	6,846 (58.3)
-Slight/moderate symptoms 2–3	1,984 (16.9)
-Moderately severe/severe symptoms(4–5)	686 (5.8)
-Unknown	2,241 (19.1)
Charlson comorbidity index	
-No (0)	3,365 (28.6)
-Moderate (1–2)	5,625 (47.8)
-Severe (≥3)	2,767 (23.5)
Length of stay (d), median (25, 75 quartiles)	13 (5, 35)
Complications after admission	

Pneumonia	
-Yes	1,030 (8.8)
-No	9,517 (81.0)
-Unknown	1,210 (10.3)
Urinary tract infection	
-Yes	1,819 (15.5)
-No	8,725 (74.2)
-Unknown	1,213 (10.3)
Pressure ulcer	
-Yes	139 (1.2)
-No	10,458 (89.0)
-Unknown	1,160 (9.9)
Falls after stroke	
-Yes	272 (2.3)
-No	10,276 (87.4)
-Unknown	1,209 (10.3)
Venous tromboembolismn	
-Yes	77 (0.7)
-No	10,495 (89.3)
-Unknown	1,185 (10.1)
Constipation	
-Yes	823 (7.0)
-No	9,626 (81.9)
-Unknown	1,308 (11.1)
Complication Yes/No	
-Yes	2,969 (25.3)
-No	7,797 (66.3)
-Unknown	991 (8.4)
Early admission to a stroke unit (by second day of admission)	
-Yes	9,660 (82.2)
-No	2,094 (17.8)
-Not relevant/contraindicated	3 (0.03)
Antiplatelet therapy (by second day of	

admission)	
-Yes	5,937 (50.5)
-No	1,298 (11.0)
-Not relevant/contraindicated	4,522 (38.5)
Anticoagulant therapy (by 14th day of admission)	
-Yes	692 (5.9)
-No	293 (2.5)
-Not relevant/contraindicated	10,772 (91.6)
Examination with CT/MRI scan (day of admission)	
-Yes	6,687 (56.9)
-No	4,670 (39.7)
-Not relevant/contraindicated	400(3.4)
Assessment by a physiotherapist (by second day of admission)	
-Yes	5,388 (45.8)
-No	4,479(38.1)
-Not relevant/contraindicated	1,890 (16.1)
Assessment by an occupational therapist (by second day of admission)	
-Yes	5,179 (44.1)
-No	4,700(40.0)
-Not relevant/contraindicated	1,878 (16.0)
Assessment of nutritional risk (day of admission)	
-Yes	5,254 (44.7)
-No	4,003 (34.1)
-Not relevant/contraindicated	2,500 (21.3)
Swallowing assessment (day of admission)	
-Yes	3,320 (28.2)
-No	3,999 (34.0)
-Not relevant/contraindicated	4,438 (37.8)
Early mobilization (day of admission)	

-Yes	6,464 (55.0)
-No	2,305 (19.6)
-Not relevant/contraindicated	2,988 (25.4)
Proportion of relevant processes of care received within time frame	
0–24	1,183 (10.1)
25–49	2,214 (18.8)
50–74	3,533(30.1)
75–100	4,827 (41.1)

*Known history or diagnosed during current admission.

†Drinks per week for men and women, respectively.

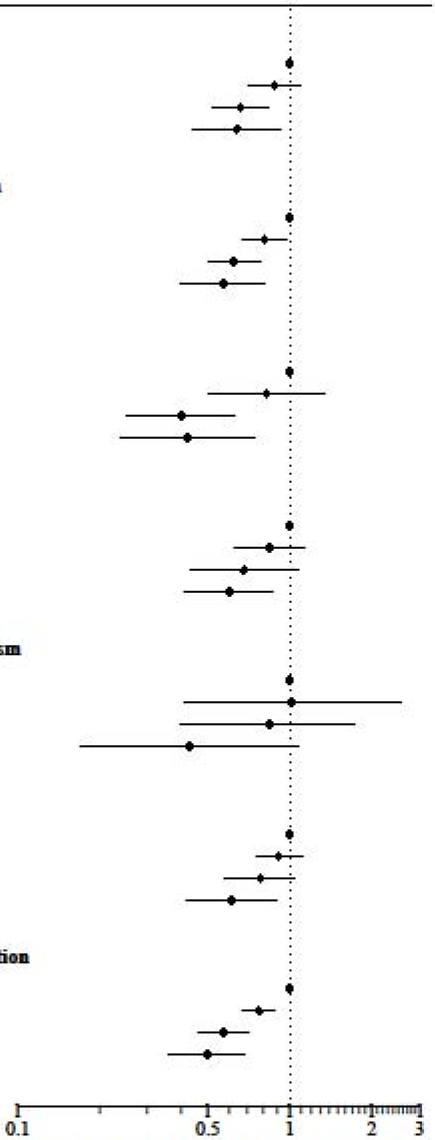
TABLE 4. Medical complications after admission for stroke according to individual processes of care received.

	Pneumonia	Urinary tract infection	Pressure ulcer	Falls after stroke	Venous thromboembolism	Constipation	Any complication
Process of care	**Adjusted OR* (95% CI)**	**Adjusted OR* (95% CI)**	**Adjusted OR * (95% CI)**	**Adjusted OR * (95% CI)**	**Adjusted OR * (95% CI)**	**Adjusted OR * (95% CI)**	**Adjusted OR * (95% CI)**
Early admission to a stroke unit	0.81 (0.66–100)	0.84 (0.69–1.01)	0.90 (0.50–1.60)	0.92 (0.75–1.13)	1.20 (0.54–2.66)	0.92 (0.78–1.08)	0.79 (0.68–0.92)
Antiplatelet therapy	0.88 (0.66–1.17)	0.94 (0.81–1.08)	1.01 (0.55–1.87)	0.99 (0.60–1.63)	0.85 (0.44–1.63)	1.20 (0.91–1.59)	0.95 (0.79–1.15)
Anticoagulant therapy	0.64 (0.46–0.88)	0.79 (0.57–1.10)	0.90 (0.50–1.62)	0.47 (0.20–1.11)	0.17 (0.05–0.55)†	0.52 (0.33–0.81)	0.59 (0.45–0.76)
Examination with CT/MRI scan	1.51 (1.20–1.91)	1.37 (1.18–1.58)	0.92 (0.61–1.39)	1.51 (1.22–1.88)	1.28 (0.80–2.07)	1.48 (1.23–1.77)	1.52 (1.35–1.72)
Assessment by a physiotherapist	1.15 (0.95–1.39)	1.04 (0.92–1.17)	0.94 (0.66–1.32)	0.93 (0.68–1.26)	1.06 (0.76–1.49)	1.05 (0.84–1.30)	1.10 (0.94–1.28)
Assessment by an occupational therapist	1.12 (0.89–1.41)	1.05 (0.89–1.24)	0.95 (0.71–1.27)	0.98 (0.79–1.21)	1.26 (0.86–1.86)	1.12 (0.89–1.40)	1.10 (0.94–1.27)
Assessment of nutritional risk	0.90 (0.74–1.10)	0.96 (0.81–1.14)	1.08 (0.69–1.70)	0.70 (0.47–1.05)	0.64 (0.29–1.44)	0.83 (0.64–1.09)	0.87 (0.70–1.07)
Swallowing assessment	0.95 (0.79–1.15)	0.96 (0.76–1.20)	1.16 (0.84–1.60)	0.95 (0.69–1.31)	0.47 (0.19–1.19)	1.00 (0.75–1.34)	0.97 (0.84–1.11)
Early mobilization	0.43 (0.34–0.54)	0.56 (0.47–0.66)	0.43 (0.22–0.84)	0.88 (0.70–1.12)	1.01 (0.57–1.78)	0.45 (0.37–0.56)	0.43 (0.35–0.53)

*All analyses are corrected for clustering of patients by department and age, sex, marital status, housing, profession, alcohol intake, smoking habits, atrial fibrillation (except for criteria on antiplatelet and anticoagulant therapy), previous stroke, Charlson comorbidity index, Scandinavian stroke scale score on admission, and other processes of care received. †Estimates not adjusted for alcohol intake and Charlson comorbidity index due to few outcomes.

FIGURE 1. Medical complications after admission for stroke according to proportion of received relevant processes of care.

Medical complications	Adjusted OR* (95% CI)
Proportion of processes of care	**Pneumonia**
0–24 %	1.00 (reference)
25–49 %	0.88 (0.70–1.10)
50–74 %	0.66 (0.52–0.83)
75–100 %	0.64 (0.44–0.93)
Test for trend	**p< 0.001**
Proportion of processes of care	**Urinary tract infection**
0–24 %	1.00 (reference)
25–49 %	0.81 (0.67–0.98)
50–74 %	0.62 (0.50–0.78)
75–100 %	0.57 (0.40–0.81)
Test for trend	**p< 0.001**
Proportion of processes of care	**Pressure Ulcer**
0–24 %	1.00 (reference)
25–49 %	0.82 (0.50–1.35)
50–74 %	0.40 (0.25–0.63)
75–100 %	0.42 (0.24–0.74)
Test for trend	**p< 0.001**
Proportion of processes of care	**Falls after stroke**
0–24 %	1.00 (reference)
25–49 %	0.84 (0.63–1.14)
50–74 %	0.68 (0.43–1.07)
75–100 %	0.60 (0.41–0.87)
Test for trend	**p = 0.019**
Proportion of processes of care	**Venous tromboembolism**
0–24 %	1.00 (reference)
25–49 %	1.02 (0.41–2.54)
50–74 %	0.84 (0.40–1.74)
75–100 %	0.43 (0.17–1.07)
Test for trend	**p = 0.145**
Proportion of processes of care	**Constipation**
0–24 %	1.00 (reference)
25–49 %	0.91 (0.75–1.11)
50–74 %	0.78 (0.58–1.05)
75–100 %	0.61 (0.42–0.90)
Test for trend	**p = 0.097**
Proportion of processes of care	**Any medical complication**
0–24 %	1.00 (reference)
25–49 %	0.77 (0.67–0.88)
50–74 %	0.57 (0.46–0.70)
75–100 %	0.50 (0.36–0.68)
Test for trend	**p< 0.001**



* All the analyses are corrected for clustering of patients by department and for age, sex, marital status, housing, profession, alcohol intake, smoking habits, atrial fibrillation (except for criteria on antiplatelet and anticoagulant therapy), previous stroke, Charlson Comorbidity Index, Scandinavian Stroke Scale Score on admission and fulfillment of one or more of the other quality of care criteria.

Appendix VI

Study III

Medical complications in patients with stroke and clinical outcome: length of stay and mortality

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ABSTRACT

Background and purpose: The relationship between in-hospital medical complications and length of stay (LOS) and mortality in patients with stroke remains unclear. We therefore examined whether medical complications are associated with LOS and mortality.

Methods: Using population-based Danish medical registries, we did a follow-up study among all patients with acute stroke admitted to stroke units in two Danish counties between 2003–2009 (n=13,721). Data regarding in-hospital medical complications, including pneumonia, urinary tract infection (UTI), pressure ulcer, falls, deep venous thrombosis (DVT), pulmonary embolism (PE), and severe constipation together with LOS and mortality were prospectively registered.

Results: Overall, 25.2 % (n=3,453) of the patients experienced one or more medical complications during hospitalization. The most common medical complications were UTI (15.4%), pneumonia (9.0%), and constipation (6.8%). Median LOS was 13 days (25th and 75th quartiles: 5, 33). All medical complications were associated with longer LOS. The adjusted relative LOS estimates ranged from 1.80 (95% confidence interval (CI): 1.54–2.11) for pneumonia to 3.06 (95% CI: 2.67–3.52) for falls. Patients with one or more complications had an increased 1-year mortality rate (adjusted Mortality Rate Ratio (MRR) 1.20, 95% CI: 1.04–1.39). The association was mainly driven by pneumonia which was associated with higher mortality both after 30-day (adjusted MRR 1.59, 95% CI: 1.31–1.93) and 1 year (adjusted MRR 1.76, 95% CI: 1.45–2.14).

Conclusions: In-hospital medical complications were associated with a longer LOS and in particular for pneumonia also associated with an increased mortality among patients hospitalized with acute stroke.

INTRODUCTION

Stroke is a leading cause of death and functional impairment.[1] In addition to the initial damage complications (neurological and medical) following acute stroke could be independent predictors for adverse outcomes.[2] All though prevention, early recognition, and management of post-stroke medical complications are considered to be essential aspects of stroke unit care, patients with acute stroke are at high risk of medical complications including pneumonia, UTI, pressure ulcer, falls, VTE, and severe constipation.[3-5] Previous studies have reported that up to 96% of all patients hospitalized with stroke experience one or more medical or neurological complications during their hospitalization.[5-15] The reported risk estimates vary substantially; however, it is evident that complications are common. Previous studies have indicated that there could be an association between medical complications and poorer outcome in patients with stroke, as complications may hinder optimum rehabilitation, extend LOS[16, 17] and have been associated with increased mortality.[5-7, 9-15, 18-22]

For effective interventions to improve patient outcomes, more detailed knowledge is needed on the impact of specific complications on clinical outcome. Existing data on this topic are limited data as most studies are often have been done on a small scale and have primarily focused on short-term outcomes.[2, 7-10, 12, 22, 23] Further, many of the existing studies have been conducted either in rehabilitation units[8, 11, 14] or in clinical trial settings.[10] There is consequently a need for large scale population-based studies on unselected patients covering the acute phase of stroke and with long-term follow-up as these patients might be more vulnerable to and influenced by complications. We therefore aimed to examine the association of in-hospital medical complications and LOS and the 30-day and 1-year mortality in patients with acute stroke in a population-based follow-up study.

METHODS

We conducted this study using Danish medical registries. Since 1968, every Danish citizen has been assigned a unique ten-digit civil registration number, which is used in all Danish registries, enabling unambiguous linkage between them.[24] The Danish National Health Service provides tax-supported health care to all residents, including free access to hospital care and general practitioners. All acute medical conditions, including stroke, are exclusively treated at public hospitals in Denmark.[25]

Study population

Patients were identified from the Danish National Indicator Project (DNIP), a nationwide initiative to document, monitor, and improve the quality of treatment and care provided by the Danish health care system for specific diseases, including stroke.[26] Participation is mandatory for all Danish hospitals treating patients for stroke.

We identified all patients admitted and discharged for acute stroke to the stroke units (n = 10) in the former Copenhagen Hospital Corporation and Aarhus County between January 13, 2003 and December 31, 2009. All patients (≥18 y old) who were admitted with stroke were eligible for inclusion in the DNIP. We only included the first stroke event registered in the study period and only patients with a valid civil registry number. In total, 13,721 admissions were available for analysis.

Medical complications

During hospital admission, data regarding the following medical complications were prospectively registered in DNIP: pneumonia, UTI, pressure ulcer, falls, venous thromboembolism (VTE), and severe constipation. Only complications that developed after hospital admission were registered. The definitions (Table 1) of the medical complications were in general in accordance with definitions previously used in other studies.[5, 7, 12]

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 another diagnosis. The discharge date was defined somewhat differently in the two study areas: in the former Copenhagen Hospital Corporation, the date was defined as the date of discharge from the stroke unit either to a rehabilitation ward, home, a nursing home, or death. In the former Aarhus County, LOS also included transfers to rehabilitation wards and therefore covered the entire hospital stay.

Mortality

Information on changes in vital status during the study's follow-up period was obtained through linkage with the Danish Civil Registration System, which since 1968 has maintained electronic records of the entire Danish population, including all persons with permanent residence in Denmark.[24] For each person registered, the Civil Registration System contains information on the civil registry number and continuously updated information on place of residence and vital status along with an additional 150 variables. For persons who have disappeared or emigrated, information on death is available only if death occurred in Denmark, or the Danish authorities were informed of the death. For all practical purposes follow-up on mortality using the Civil Registration system can be considered fully complete.

Patient characteristics

Data regarding the following patient characteristics were collected at the time of hospital admission: age, sex, marital status (living with partner, family, or friend or living alone), housing (own home, nursing home, or other institution), profession at admission (employed, unemployed, or pensioner), Scandinavian stroke scale (SSS) score, Charlson comorbidity index (0, no comorbidity; 1–2, low comorbidity; ≥3, high comorbidity), previous stroke, previous and/or current atrial fibrillation, hypertension (yes/no) preadmission modified Rankin score, smoking habits (current, former (>1/2year), or never), and alcohol intake (≤21/14 and >21/14 drinks per week for men and women, respectively).

The SSS score was used to assess admission stroke severity.[27] This scale is a validated and widely used neurological stroke scale in Scandinavia that evaluates level of consciousness; eye movement; power in the arm, hand, and leg; orientation; aphasia; facial paresis; and gait with a total score that ranges from 0 to 58. The SSS score can be assessed reliably either face-to-face or from routine hospital admission records.[28]

The preadmission modified Rankin score reflects the patients' functional ability prior to the stroke. The scale grades the patients from grade 0 (no symptoms) to grade 5 (severe disability) with a moderate inter-observer agreement.[29]

Information on processes of in-hospital care during the acute phase, which have been linked with mortality and LOS,[30, 31] was obtained from the DNIP and included data on fulfillment of nine processes of care.[26] The processes of care were: early admission to a specialized stroke unit, early administration of antiplatelet or anticoagulant therapy, early examination with CT/MRI scan and early assessment by a physiotherapist, an occupational therapist, of nutritional risk, and of swallowing function, and early mobilization. We computed a variable containing the percentage of fulfilled processes of care for each patient as a measure for the quality of in-hospital stroke care. We also computed the Charlson comorbidity index score for each patient based on all of the discharge diagnoses recorded before the hospitalization for stroke.[32] We used an adapted version of the index that utilizes ICD codes by identifying all hospital diagnoses for each patient from 1994 onwards in The Danish National Registry of Patients.[33]

Data regarding previous hospitalizations were obtained from the National Registry of Patients, which contains the data for all discharges from all nonpsychiatric hospitals in Denmark since 1977.[34] The Charlson comorbidity index covers 19 major disease categories and has been reported to be useful for patients with stroke.[35] The study was approved by The Danish Data Protection Agency (J.no.2007-41-0563).

Statistical analysis

First, we examined the association between the individual medical complication and LOS by linear regression. A natural log (ln) transformation was used to correct for the right skewness of LOS.[36] When reporting the findings of the analyses, we transformed the regression estimates back into the original units by exponentiating the estimates and thereby, obtained the ratios of the geometric means of LOS.

Follow-up started on the hospital admission date and ended after 30-day (or 1-year) or end of the study period. Cox proportional hazard regression analyses were used to obtain MRRs and 95% CI for mortality within 30-days or 1 -year after stroke according to each medical complication, adjusted for all of the above-mentioned patient characteristics. Age and SSS score were included as natural cubic splines. We used a random-effects model to correct for possible clustering by department in all analyses[37] because unmeasured characteristics of the department, including other aspects of quality of care than the processes adjusted for in this study, might be associated with patient mortality.

A total of 7,032 patients (51.25%) had missing data on one or more of the following variables: marital status, housing, profession, alcohol intake, smoking habits, atrial fibrillation, hypertension, previous stroke, Rankin score and SSS score. We therefore used multiple imputation to impute missing values of the patient characteristics assuming that data was missing at random.[38, 39] We imputed five datasets using the following variables: age, sex, marital status, housing, profession at admission, alcohol intake, smoking habits, atrial fibrillation, hypertension, SSS score, preadmission modified Rankin score, the Charlson comorbidity index score, previous stroke, stroke subtype, stroke unit identifier, proportion of relevant processes of care received. In addition, we also included the event indicator and the Nelson-Aalen estimator of the cumulative hazard to the survival time in the imputation model. Finally, we performed some additional analyses to evaluate the robustness of our findings. First, we replicated the analyses of LOS stratified by discharge status (dead/alive at discharge) and secondly according to geographic area (Copenhagen, Aarhus). Thirdly, we stratified the analyses according to age, sex, and SSS score to assess whether these acted as effect modifiers on the association between medical complications and LOS or mortality. For all estimates, a 95% CI was calculated. STATA version 11.0 (StataCorp LP, College Station, TX, USA) was used to perform the analyses.

RESULTS

Table 2 summarizes patient characteristics as well as cumulative risk of medical complications and processes of care received among the 13,721 patients. A total of 25.2 % (*n* =3,453) of the patients experienced at least one medical complication during their hospitalization. The most frequent complications were UTI (15.4%), pneumonia (9.0%), and constipation (6.8%). Median LOS was 13 days (25th and 75th quartiles: 5, 33).

Table 3 presents the unadjusted and adjusted relative LOS according to the individual medical complication present. All complications were associated with longer LOS and these associations remained after adjusting for a wide range of possible confounding factors including proportion of relevant processes of care received and correction for clustering of patients by department. Adjusted relative LOS ranged from 1.80 (95%l (CI): 1.54–2.11) for pneumonia to 3.06 (95% CI: 2.67– 3.52) for falls after stroke.

The overall 30-day mortality rate was 8.9%, and the overall 1-year mortality rate was 21.0 %.

Figure 1 shows that patients who experienced at least one medical complication had an increased mortality after 1-year compared with patients who did not experience any of the complications. This association remained after adjusting for possible confounding factors (adjusted MRR 1.20, 95% CI: 1.04– 1.39).

Table 4 shows adjusted MRRs according to the individual medical complications. Pneumonia (adjusted MRR 1.59, 95% CI: 1.31–1.93) and VTE (adjusted MRR 1.49, 95% CI: 0.75– 2.96) were associated with higher 30-day mortality although the association did not reach statistical significance in the case of VTE. UTI, falls after stroke, and constipation were all associated with significant lower risk of 30-day mortality with adjusted MRRs ranging from 0.21–0.74, whereas no clear association with 30-day mortality was found for pressure ulcer.

The highest 1-year mortality rate was found among patients with pneumonia (adjusted MRR 1.76, 95% CI: 1.45–2.14) and pressure ulcer (adjusted MRR 1.47, 95% CI: 1.17– 1.85), respectively.

In contrast, patients experiencing falls after stroke and constipation had a lower 1-year mortality compared to patients without any medical complications.

DISCUSSION

We found that patients with stroke experiencing in-hospital medical complications in general had longer LOS and a higher 30-day and 1- year mortality.

The increased mortality among patients with medical complications was mainly related to pneumonia.

Strengths and limitations

The strengths of our study include the population-based design, the availability of prospectively collected detailed data, and the large number of patients included. As always in observational studies, possible unaccounted (e.g., use of secondary medical prophylaxis after discharge) and residual confounding is a concern. However, several measures were taken to minimize the impact of possible confounding, including control for a wide range of well-established prognostic factors (e.g., stroke severity), as well as correction for clustering at the individual stroke units. It is well known that misclassification can occur during data collection in routine clinical settings. Still, thorough efforts are made to ensure the data validity in DNIP.[26] Regular structured audits are conducted nationally, regionally, and locally, which include validation of the completeness of patient registration against hospital discharge registries. Furthermore, we have examined the validity of the medical complications registered in the DNIP and found a high specificity (i.e., 97.3% (95% CI 96.7–97.8)) and reasonable overall positive predictive value (i.e., 71.7 % (95% CI 67.4–75.8)).[40]

Comparison with other studies

Despite differences in study design, sample sizes, study settings and definition of medical complications and length of follow-up, our finding of an association between medical complications and a higher risk of adverse outcome appears to support results from a number of previous studies.[6, 16, 17, 21, 41-46]

The significantly longer LOS for patients with medical complications found in our study is in agreement with a number of studies.[6, 17, 41, 44, 47] In line with our findings, these previous studies generally found that infections particularly were associated with longer LOS.[43, 45, 46, 48, 49] However, data are limited on the role of other types of medical complications including pressure ulcer, falls, DVT**,** PE, and constipation. Yet, our results identifying an increased LOS for patients experiencing falls agree with those of Czernuszenko et al, who found that the probability of experiencing a first fall increases with LOS.[50] Furthermore, in accordance with a Chinese study, we found that patients with constipation stayed longer in the hospital than those without constipation.[47]
Interpretation of observational data on complications and LOS is in general a challenge as pointed out in earlier studies, where medical complications were also associated with longer LOS among patients with acute stroke.[43,44,16] Thus, it is difficult with certainty to determine whether longer LOS is caused by medical complications or whether longer LOS caused the complications. This challenge is also present in our study and should be kept in mind when interpreting the findings. However, the fact that most of the medical complications appear to develop early after hospital admission supports the hypothesis that medical complications *per se* may increase LOS.[36]
A number of studies have examine the association between medical complications and mortality including in-hospital,[7, 9, 11-13, 15, 42, 43, 48, 51, 52], 30-day.[6, 20, 22, 53-56] or overall mortality.[5, 12, 44, 55, 57, 58] The different length of follow-up and different levels of control of possible confounding factors (several studies have only reported unadjusted risk estimates) used in the studies makes it difficult to compare our results directly with all of the existing studies.

The present study found an increased 1- year mortality in those with at least one complication compared with those without complications, which is in accordance with the results from Bae et al, who in 2005 reported an increased risk (adjusted OR 1.94 (1.14–3.29) for those patients who experienced a complication.[6]

In their 1996 paper, Davenport et al found that medical complications were associated with an increased risk of death during the hospital stay (unadjusted OR: 1.9; (95% CI: 1.2–2.9)) (multivariate statistics were not included in the analyses).[7] In a 1998 study by Johnston et al the authors concluded that medical complications accounted for 50% of deaths three months after stroke.[10] In 2004, Heuschmann et al in a large registry-based study involving 13,440 patients with ischemic stroke confirmed the findings of Davenport et al and Johnston et al.[9] In that study the authors found that more than 50% of all in-hospital deaths were caused by serious medical or neurological complications.[9]

Several researchers have investigated the associations between post-stroke infection and clinical outcome, and our findings are in accordance with previous studies that found that infections, pneumonia particularly, were associated with an increased risk of both short- and long-term morality. These studies found that death occurring in the following weeks after an acute stroke was mainly related to infections like pneumonia.[7, 9-11, 20-22, 45, 48, 51, 53, 56, 58] Katzan at al found that pneumonia was a leading cause of death in the post-acute phase of stroke accounting for approximately 30% of the 30-day mortality.[20] This result was confirmed by Heuschmann et al (2004) that identified pneumonia as the complication with the highest attributable proportion of death in the entire stroke population, accounting for 31% of all in-hospital deaths.[9] Finally, Vermeij et al estimated the increased risk of mortality at 1 year in patients with post-stroke pneumonia to be doubled.[21, 56] The finding of pneumonia being a strong predictor of mortality suggests that proper management of pneumonia could improve short- and long-term prognosis for patients with acute stroke.

However, available data on UTI are more sparse. Interestingly we found lower adjusted mortality risk estimates (MRRs) after UTI than did other studies. Although in some of the studies the increased risk of mortality did not reach statistically significance.[13, 51, 53, 59] Our findings, however, are in the same direction as some studies that showed that UTI was associated with a lower risk of in-hospital mortality.[43,45]

VTE was associated with a higher 30-day and 1-year mortality in our study, although it did not reach statistically significance. This result is partly in agreement with previous studies that have identified VTE as an important contributor to mortality in patients with stroke.[9, 60]

Our findings of decreased risk of 30-day mortality in patients (treated in a stroke unit) with falls, and constipation after stroke are partly in accordance with a study that indicated that stroke unit care appeared to reduce the risk of death attributable to complications of immobility.[4] However, very sparse information exists on the impact of pressure ulcer, falls and constipation after stroke and mortality. The explanation for this is not entirely clear, but the findings indicate that stroke units are effective settings for detecting and treating medical complications at an early stage. Patients with complications could possibly also receive an even closer monitoring during the remaining part of their hospitals stay which could contribute to the lower mortality compared to patients without the mentioned medical complications. This observation adds to our understanding of the stroke units. It has though been known for many years that stroke unit care reduces the risk of death after stroke, but how this benefit is achieved, is unclear. It has been suggested that some of the survival benefit of stroke unit care may be explained by a reduction in the risk of complications,[61] and by earlier initiation of rehabilitation[61], and mobilization and by careful monitoring of clinical parameters[18, 62, 63]

Effective treatment of medical complication should maybe also be added to the list although a more firm conclusion on this topic would require a formal comparison with stroke patients not admitted to stroke units.

In conclusion in our large population-based follow-up study we found that patients hospitalized with medical complications had significantly longer LOS than did patients without complications. In-hospital complications were also in particular for pneumonia associated with an increased mortality.

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TABLE 1. Definitions of the medical complications

Medical complication	Definition
Pneumonia	Description of clinical indications or positive chest radiograph
Urinary tract infection	Clinical symptoms of urinary infection combined with a positive culture and resistance examination (D+R positive with significant bacteriuria (>10^5/ml).
Pressure ulcer	Any skin break or necrosis documented in the medical record as symptoms resulting from pressure.
Falls after stroke	Any documented fall regardless of cause. It should be documented that the accident was inadvertent, and that the patient inadvertently fell down; i.e., with or without bed rest.
Venous thromboembolism	Either having clinical indication(s) of deep vein thrombosis supported by objective examination, or clinical indication(s) of pulmonary embolism supported by objective examination.
Constipation	Clinical symptoms combined with requirement for oil phosphate clysma (enemas).

TABLE 2. Descriptive characteristics of 13,721 patients with acute stroke admitted to stroke units in the Copenhagen and Aarhus areas between 2003-2009.

Characteristics	N (%)
Age (y)	
18–65	3,485 (28.7)
>65–80	5,006 (41.2)
>80	3,650 (30.1)
Mean age(years)	72
Median (range)	74(18, 107)
Sex	
-Men	6,877 (50.1)
-Women	6,844 (49.9)
Marital status	
-Living with partner, family, or friend	6,066 (44.2)
-Living alone	6,921 (50.4)
-Other	362 (2.6)
-Unknown	372 (2.7)
Housing	
-Own home	12,131 (88.4)
-Nursing home or other institution	965 (7.0)
-Other	218 (1.6)
-Unknown	407 (3.0)
Profession at admission	
-Employed/unemployed	2,347 (17.1)
-Pensioner	9,948 (72.5)
-Other form of profession	181 (1.3)
-Unknown	1,245 (9.1)
Type of stroke	
-Intracerebral hemorrhage	1,529 (11.1)
-Ischemic	10,897 (79.4)
-Unspecified	1,295 (9.4)
Scandinavian Stroke Scale on admission	
-Very severe, 0–14 points	1,100 (8.0)
-Severe, 15–29 points	1,183 (8.6)

-Moderate, 30–44 points	2,124(15.5)
-Mild, 45–58 points	5,334 (38.9)
-Unknown	3,980 (29.0)
Previous stroke	
-Yes	2,984 (21.8)
-No	10,040 (73.2)
-Unknown	697 (5.1)
Atrial fibrillation*	
-Yes	2,551 (18.6)
-No	10,521 (76.7)
-Unknown	649 (4.7)
Hypertension*	
-Yes	7,328 (53.4)
-No	5,594 (40.8)
-Unknown	799 (5.8)
Smoking habits	
-Current	4,859 (35.4)
-Former	2,679 (19.5)
-Never	3,821 (27.9)
-Unknown	2,362 (17.2)
Alcohol intake†	
-≤21/14 drinks/week	10,350 (75.4)
->21/14 drinks/week	1,223 (8.9)
-Unknown	2,148 (15.7)
Rankin score (before admission)	
-No/no significant symptoms 0–1	7,969 (58.1)
-Slight/moderate symptoms 2–3	2,351 (17.1)
-Moderately severe/severe symptoms(4–5)	788 (5.7)
-Unknown	2,613 (19.4)
Charlson comorbidity index	
-No (0)	3,871 (28.2)
-Moderate (1–2)	6,545 (47.7)
-Severe (≥3)	3,305 (24.1)
Length of stay (d), median (25, 75 quartiles)	13 (5, 33)
Complications after admission	

Pneumonia	
-Yes	1,235 (9.0)
-No	11,055 (80.6)
-Unknown	1,431 (10.4)
Urinary tract infection	
-Yes	2,107 (15.4)
-No	10,164 (74.1)
-Unknown	1,450 (10.6)
Pressure ulcer	
-Yes	163 (1.2)
-No	12,194 (88.9)
-Unknown	1,364 (9.9)
Falls after stroke	
-Yes	288 (2.1)
-No	12,021 (87.6)
-Unknown	1,412 (10.3)
Venous tromboembolismn	
-Yes	86 (0.6)
-No	12,240 (89.2)
-Unknown	1,395 (10.2)
Constipation	
-Yes	935 (6.8)
-No	11,260 (82.1)
-Unknown	1,526 (11.1)
Complication Yes/No	
-Yes	3,453 (25.2)
-No	9,075 (66.1)
-Unknown	1,193(8.7)
Early admission to a stroke unit (by second day of admission)	
-Yes	11,357 (82.8)
-No	2,361 (17.2)
-Not relevant/contraindicated	3 (0.02)
Antiplatelet therapy (by second day of admission)	

-Yes	7,081 (51.6)
-No	1,424 (10.4)
-Not relevant/contraindicated	5,216 (38.0)
Anticoagulant therapy (by 14th day of admission)	
-Yes	800 (5.8)
-No	335 (2.4)
-Not relevant/contraindicated	12,586 (91.7)
Examination with CT/MRI scan (day of admission)	
-Yes	8,126 (59.2)
-No	5,172 (37.8)
-Not relevant/contraindicated	423(3.1)
Assessment by a physiotherapist (by second day of admission)	
-Yes	6,447 (47.0)
-No	5,064(36.9)
-Not relevant/contraindicated	2,210 (16.1)
Assessment by an occupational therapist (by second day of admission)	
-Yes	6,192 (45.6)
-No	5,325(38.8)
-Not relevant/contraindicated	2,204 (16.1)
Assessment of nutritional risk (day of admission)	
-Yes	6,282 (45.8)
-No	4,555 (33.2)
-Not relevant/contraindicated	2,884 (21.0)
Swallowing assessment (day of admission)	
-Yes	4,217 (30.7)
-No	4,757 (34.7)
-Not relevant/contraindicated	4,747 (34.6)
Early mobilization (day of admission)	
-Yes	7,472 (54.5)
-No	2,559 (18.6)

-Not relevant/contraindicated	3,690 (29.9)
Proportion of relevant processes of care received within time frame	
0–24	1,252 (9.1)
25–49	2,279 (16.6)
50–74	3,923(28.6)
75–100	6,267 (45.7)

*Known history or diagnosed during current admission.

†Drinks per week for men and women, respectively.

TABLE 3. Medical complications and length of stay (LOS).

Medical complication	N (%)	Median LOS (25th and 75th Quartiles) Complication respectively = No	Median LOS (25th and 75th Quartiles) Complication respectively = Yes	Unadjusted Ratio of LOS (95% CI)	Adjusted Ratio of LOS* (95% CI)
Pneumonia	1,235 (9.0)	11 (4, 28)	31 (14, 60)	2.41 (1.91–3.05)	1.80 (1.54–2.11)
Urinary tract infection	2,107 (15.4)	10 (4, 25)	36 (16, 64)	3.12 (2.25–4.32)	2.29 (1.88–2.80)
Pressure ulcer	163 (1.2)	13 (5, 32)	48 (26, 74)	3.34 (2.20–5.06)	1.98 (1.53–2.55)
Falls after stroke	288 (2.1)	12 (5, 31)	56 (31, 86)	4.33 (3.24–5.78)	3.06 (2.67–3.52)
Venous thromboembolism	86 (0.6)	13 (5, 32)	56 (25, 99)	3.73 (2.65–5.25)	2.40 (1.96–2.95)
Constipation	935 (6.8)	11 (5, 28)	45 (25, 73)	3.80 (.2.82–5.11)	2.66 (2.23–3.16)
Any complication	3,453 (25.2)	9 (4, 21)	33 (15, 62)	3.29 (2.45–4.14)	2.48 (2.01–3.06)

*All analyses are corrected for clustering of patients by department and age, sex, marital status, housing, profession, alcohol intake, smoking habits, atrial fibrillation, previous stroke, hypertension, Charlson comorbidity index, Scandinavian stroke scale score on admission, type of stroke, and relevant processes of care received.

TABLE 4. Medical complications and 30-day and 1-year all cause mortality.

		30-day mortality rates			1 - year mortality rates		
Medical complication	**N (%)**	**30-day mortality** N (%)	**Unadjusted MRR (95% CI)**	**Adjusted MRR * (95% CI)**	**1-year mortality N (%)**	**Unadjusted MRR* (95% CI)**	**Adjusted MRR* (95% CI)**
Pneumonia	1,235 (9.0)	307/1218 (25.2)	4.43 (3.57–5.50)	1.59 (1.31–1.93)	628/ 2,886 (21.8)	4.07 (3.43–4.80)	1.76 (1.45–2.14)
Urinary tract infection	2,107 (15.4)	153/1218 (12.6)	0.88 (0.69–1.12)	0.45 (0.38–0.54)	669/ 2,886 (23.2)	1.91 (1.73–2.11)	0.94 (0.84–1.05)
Pressure ulcer	163 (1.2)	22/1218 (1.8)	1.64 (1.03–2.62)	0.74 (0.42–1.30)	88/ 2,886 (3.1)	3.20 (2.62–3.90)	1.47 (1.17–1.85)
Falls after stroke	288 (2.1)	76/1218 (0.6)	0.27 (0.13–0.56)	0.21 (0.10–0.47)	68/ 2,886 (2.4)	1.11 (0.99–1.25)	0.82 (0.68–0.99)
Venous thromboembolism	86 (0.6)	15/1218 (1.2)	2.24 (1.30–3.84)	1.49 (0.75–2.96)	30/ 2,886 (1.0)	1.93 (1.14–3.29)	1.28 (0.71–2.29)
Constipation	935 (6.8)	45/1218 (3.7)	0.54 (0.35–0.83)	0.38 (0.28–0.50)	260/ 2,886 (9.0)	1.41 (1.18–1.69)	0.87 (0.76–0.99)
Any complication	3,453 (25.2)	426/1218 (35.0)	1.79 (1.40–2.29)	0.78 (0.65–0.95)	1,201/ 2,886 (41.6)	2.53 (2.18–2.95)	1.20 (1.04–1.39)

*All analyses are corrected for clustering of patients by department and age, sex, marital status, housing, profession, alcohol intake, smoking habits, atrial fibrillation, previous stroke, hypertension, Charlson comorbidity index, Scandinavian stroke scale score on admission, type of stroke, and proportion of relevant processes of care received.

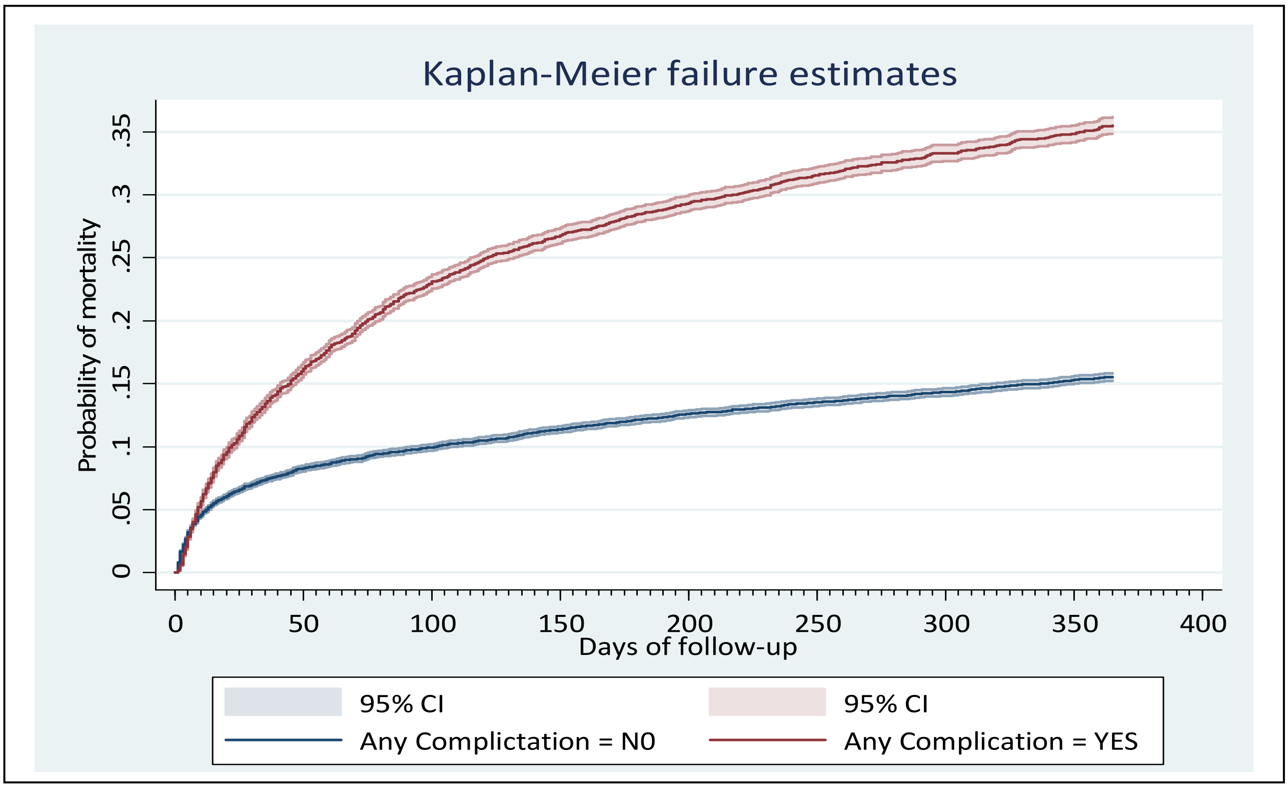

Figure 1. Cumulative mortality curves of one year all-cause mortality after hospitalization with acute stroke among patients with and without in-hospital medical complications.

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