Survival after stroke

Risk factors and determinants in the Copenhagen Stroke Study

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This review has been accepted as a thesis together with eight previously published papers by University of Copenhagen 26th of March 2010 and defended on 9th of June 2010

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Dan Med Bull 2010;57:(10)B4189

LIST OF PAPERS INCLUDED IN THIS DOCTORAL THESIS

1) Jørgensen HS, Kammersgaard LP, Nakayama H, Raaschou HO, Larsen K, Hübbe P, Olsen TS. Treatment and rehabilitation on a stroke unit improves 5-year survival. A community-based study. Stroke 1999; 30(5):930-933.
2) Jørgensen HS, Kammersgaard LP, Houth J, Nakayama H, Raaschou HO, Larsen K, Hübbe P, Olsen TS. Who benefits from treatment and rehabilitation in a stroke Unit? A community-based study. Stroke 2000; 31(2):434-439.
3) Kammersgaard LP, Jørgensen HS, Nakayama H, Reith J, Raaschou HO, Olsen TS. Leukocytosis in acute stroke: Relation to initial stroke severity, infarct size, and outcome: The Copenhagen stroke study. J Stroke Cerebrovasc Dis 1999; 8(4):259-263.
4) Kammersgaard LP, Rasmussen BH, Jørgensen HS, Reith J, Weber U, Olsen TS. Feasibility and safety of inducing modest hypothermia in awake patients with acute stroke through surface cooling: A case-control study: the Copenhagen Stroke Study. Stroke 2000; 31(9):2251-2256.
5) Kammersgaard LP, Jørgensen HS, Reith J, Nakayama H, Houth JG, Weber UJ et al. Early infection and prognosis after acute stroke: the Copenhagen Stroke Study. J Stroke Cerebrovasc Dis 2001; 10(5):217-221.
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7) Kammersgaard LP, Jørgensen HS, Reith J, Nakayama H, Pedersen PM, Olsen TS. Short- and long-term prognosis for very old stroke patients. The Copenhagen Stroke Study. Age Ageing 2004; 33(2):149-154.
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SELECTED ABBREVIATIONS AND ACRONYMS

HR:	Hazard Ratio
OR:	Odds Ratio
CI:	Confidence Interval
BI:	Cerebral Infarction
ICH:	Primary Intracerebral Hemorrhage
AF:	Atrial Fibrillation
AH:	Arterial Hypertension
DM:	Diabetes Mellitus
PAD:	Peripheral artery disease
IHD:	Ischemic Heart Disease
SSS:	Scandinavian Stroke Scale
NIHSS:	National Institute of Health Stroke Scale
MRI:	Magnetic Resonance Imaging
CT:	Computerized Tomography
CHD:	Coronary heart disease
SU:	Stroke Unit
GMW:	General Medical Ward
INR:	International Normalized Ratio

SUMMARY

The eight papers included in this doctoral thesis were made during my position as a clinical research assistant at the Department of Neurology, Bispebjerg Hospital. All papers are based on the Copenhagen Stroke Study, which comprises a cohort of 1197 patients with acute stroke admitted to a single stroke unit and recruited from a well-defined area in Copenhagen, Denmark. This thesis focuses on the survival after stroke in relation to several baseline clinical characteristics and risk factors for cardiovascular disease. The thesis comes in three sections with regard to whether factors or clinical characteristics are permanent, potentially modifiable, or possible to change. The relative importance of the factors and clinical characteristics are discussed in relation to short-, intermediate-, and long-term survival after stroke. The results from the Copenhagen Stroke Study are compared to the results from other community-based or population-based studies. The two most prominent factors that determine both short- and long-term survival after stroke are age and stroke severity at onset. Advancing age and increasing severity are perceptively negatively correlated to survival. In some cases emerging therapies such as thrombolytic therapy and hypothermia may alleviate the burden of stroke severity, but this is not the case for the majority of stroke patients. The necessity to measure stroke severity with a validated stroke scale when comparing stroke patients in randomized clinical trials or population-based surveys is emphasized. For factors such as sex, and most cardiovascular risk factors further studies are necessary to clarify the relation to

survival because studies disagree. Conclusions from studies of the relation between survival and alcohol intake are still debatable, mostly because of diverging definitions of the intensity of exposure. Smoking is uniformly associated with a poorer survival after stroke. Stroke unit treatment improves both short- and long-term survival regardless of stroke type, severity, age, and cardiovascular risk factor profile.

INTRODUCTION

Stroke continues to be a major public concern in Denmark, with more than 10 000 incident strokes occurring each year (1;2). In Denmark, as well as in other Western European countries, stroke remains the third leading cause of death after heart disease and cancer. Furthermore, stroke is the single most prominent brain disease contributing to years of life lost when the burden of neurological, neurosurgical, and psychiatric diseases are considered together (3). It is to be anticipated that the projected increase in the elderly population, with improvements in life expectancy, will further increase stroke prevalence and it overall burden for the populations of industrialized countries. On the other hand, there have been countervailing developments in the identification and treatment of risk factors for stroke and in the treatment of acute stroke (4-10). Studying individual risk factors and stroke characteristics can provide new insights about their varying influences on short term (within 30 days), intermediate (from 30 days to 1 year) and long term survival after stroke. The Copenhagen Stroke Study is one of the few prospective and community based studies providing a lengthy follow-up of a large cohort of unselected stroke patients.

In this review, survival after stroke is discussed in relation to factors that can be considered irreversible, potentially modifiable, or modifiable. Factors that are irreversible include age, sex, stroke type, stroke characteristics (aphasia, anosognosia, neglect, apraxia, and dementia), and marital status. Despite the development in the past decade of thrombolytic therapy for acute ischemic stroke, stroke severity remains impossible to alleviate in the vast majority of patients. The modifiable factors do not exclusively include crude and well-established cardiovascular risk factors such as atrial fibrillation, diabetes, arterial hypertension, ischemic heart disease, and intermittent claudication, but also life-style related factors. The latter include smoking and alcohol consumption. Recent advances in stroke treatment have added antiplatelets and lipid-lowering agents to the battery of modifiable factors that might improve stroke recovery and survival.

IRREVERSIBLE FACTORS

Age:

The overall mortality after stroke rises steeply with age (11-28). The risk for the oldest patients (>or= 85years) of dying within 30 days after stroke is reported to be from 25% to over 50% (13-17;19;24;26;28), while the risk of dying one year after stroke is reported to range from 50% to more than 90% (11;12;14;17;25-27;29). However, the adverse effect of advancing age on survival after stroke may not only relate to the effect of age per se. Advancing age is also associated with changes in other prognostic variables such as more severe strokes (14;18;19;30), higher frequency of atrial fibrillation (14;20;30;31), and more prevalent pre-stroke disability (14;30). On the other hand older age is less often associated with hypertension (14;30), diabetes (14;30), and smoking (14;30). Several studies have reported the influence of age on stroke survival adjusted for differences in other prognostic variables (12;14;15;18;19;24;26;28;29;32-39) [table 1], but not all adjusted for onset stroke severity (26;29;33;38), instead surrogate measurements for stroke severity such as level of consciousness, severity of hemiparesis etc. were used (11;12;15;19;28;34;37), or studies employed a scale not validated or suitable for measuring neurological deficits in stroke patients (11;32;36;39). Only three studies dedicated to study age used validated stroke scales such as the NIHSS (35) or the SSS score (14;18). In the Copenhagen Stroke Study one early report found that age had no independent impact on survival within 3 months after onset (18). However in another study with a lengthy follow-up we found that very old age (>or= 85 years) as opposed to younger age was a strong predictor of short and long-term mortality after stroke (HR 2.0; 95% CI, 1.6 to 2.5) independent of other prognostic variables (14). In another study we found that advancing age was associated with increased long-term mortality (HR, 1.69 per 10-year increase; 95% CI, 1.43 to 2.00) for 390 stroke patients (both ICH and BI) admitted within 6 hours of stroke onset (40), independent of differences in risk factor profile. In the same study, age appeared to become increasingly significant for mortality when patients that died within three months after stroke were excluded (HR, 1.85 per 10-year increase; 95% CI, 1.51 to 2.26) (40). This suggests that the influence of age on post stroke survival might be changing over time, because in the early stages after onset other acute factors reduce the influence of age on survival.

Sex:

Numerous studies have explored the influence of male or female sex on survival after stroke (11;12;16;17;25;26;29;33;35-39;41-54) [table 2]. Most studies report that sex has no influence on survival (11;12;16;25;26;29;33;35;37-39;41-44;49-54), which is a surprising finding because of the considerably longer life expectancy for women (55). Three studies found survival significantly better for men than for women (42;45;48), and four studies reported survival for women to be better (17;36;46;47). The disagreement when comparing studies is partly explained by the differences in study design, sample size and follow-up. Recently, one study with a very large sample size and a five-year follow-up reported that survival for men and women varies with time after stroke (46). In that study the adjusted mortality was lower for women than for men during the first month after stroke onset, while the opposite relation was found during the second month, and after the third month survival was again in favor of women. But there are also gender specific variations in severity of stroke, risk factor profile, and demographic characteristics that also must be taken into account when creating reliable comparisons of survival between men and women. Stroke severity was measured in only a minority of studies analyzing the influence of sex on post stroke survival (12;25;35;37;39;43;46;47;54), but only four studies used validated stroke severity scales when adjusting for other relevant confounders (35;46;47;54). A Swedish study found identical rates for one-year adjusted survival (35), while two Danish studies found better long-term survival for women (46;47). In the Copenhagen Stroke Study, survival for men and women was studied 10 years after stroke in 999 patients (47). Women had more severe strokes, were older, had more often pre-existing disability, and ICH prior to stroke onset. However, women were less likely to be smokers or daily alcohol consumers. This study showed a cut-off point in survival 9 months after stroke onset where sex became a significant independent predictor of survival.

Within 9 months after stroke onset, adjusted survival was equal in men and women, while survival thereafter became increasingly significant in favor of women over time.

Type of Stroke:

Patients with ICH are generally considered to carry a greater mortality risk than patients with BI (29;43;56-67) [table 3]. Most studies have measured 28 to 30 day case-fatality and reported unadjusted fatality rates for BI between 10.9% and 26.0% as compared to fatality rates for ICH between 28.9% 61.0% (43;56-66). Two studies reported 3-months case-fatality rates of 18.4% to 20.1% versus 45.2% to 50.0% for BI and ICH respectively (59;60). Three studies reported 1-year case-fatality rates for BI between 26% and 31.6% and for ICH between 39% and 62% (43;59;67). These variations in case fatality rates were due to differences in study designs and the number of patients included, and reflect that studies were conducted in different periods of time. Only one Japanese study with a lengthy follow-up of ten years reported long-term mortality after stroke and found ICH to be an independent predictor of long-term mortality after stroke. That study considered subarachnoid hemorrhages and ICH together, did not take stroke severity into account, and included only 333 patients with stroke (29). Comparison between hemorrhagic and ischemic stroke in population-based studies is hampered by the unequal distribution of the two types of stroke, because BI is 10 times more frequent than ICH (43;56-64;66;68;69), which makes it necessary to study large stroke populations to facilitate statistical evaluation. Furthermore, since stroke is generally more severe in ICH than in BI, severity at stroke onset must be measured and accounted for (68). In the Copenhagen Stroke Study the relative frequency of ICH increased with stroke severity from 3.6% in patients with mild strokes to 26.4% in those with very severe strokes (68).This study concluded that survival in ICH is poorer because of the more severe strokes in ICH compared to stroke severity among patients with BI. However, survival was restricted to the in-hospital period, and thus did not provide a lengthy follow-up (68). In a case-control study of 120 ICH patients compared with 120 patients with BI matched for age and Glasgow-coma scale there was no difference in survival after one year (70). In the Copenhagen Stroke Study we found that stroke type had no independent predictive influence on mortality several years after stroke onset in a Cox proportional hazard analysis adjusted for variations in age, risk factor profile, and stroke severity (14). In the majority of studies (29;43;56-63;66;69) stroke severity was not measured and therefore was not taken into account, which perhaps is the most important reason for the different findings when comparing studies.

The two types of stroke; intracerebral hemorrhage and ischemic stroke, share some of the risk factors for stroke, and the association of atrial fibrillation, ischemic heart disease, and diabetes with BI seem well established in studies comparing ICH and BI. But the implication of risk factors such as hypertension, smoking, and alcohol consumption in relation to stroke type remain controversial (68;71-75).

Further larger studies with a longer follow-up are required to study differences and similarities between patients with ICH and BI in respect to risk factors, stroke severity, and other determinants of survival.

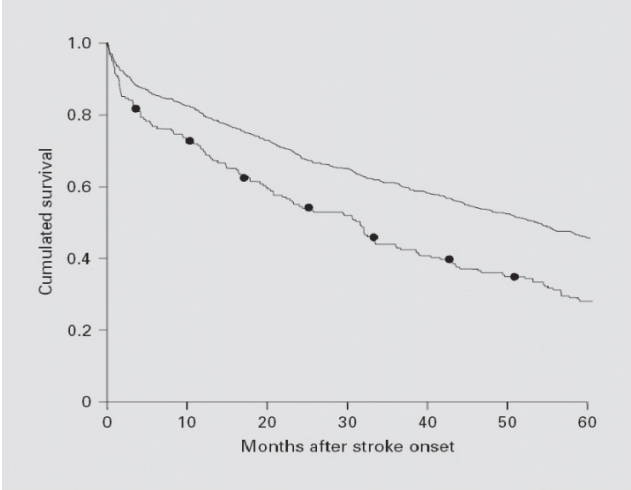

Figure 1

Kaplan-Meier survival plot for patients with ●—● versus without —— previous stroke (n = 869; p < 0.0001).

Previous Stroke:

A history of at least one previous stroke may suggest a higher risk for another cerebrovascular event and is therefore considered a risk factor for stroke (76). According to the Northern Manhattan Stroke Study the risk for a subsequent stroke is 6% within 30 days after onset, 12% within the first year, and 25% within five years following a stroke (77). In community-based studies somewhere between 20% and 30% of patients with acute stroke have had a previous stroke (15;34;36;49;54;78;79). The significance of an earlier stroke for the prognosis after a subsequent stroke is not very well known, because studies reporting on survival after stroke in relation to previous stroke as a risk factor are still limited (12;15;25;34;36;43;54;78;79) [table 4]. Two large scale studies reported that a history of previous stroke was a predictor of in-hospital mortality (15) and mortality six months after stroke (36) independent of other risk factors, age, and stroke severity. Similar results have been reported for long-term survival after stroke in relation to previous stroke as a risk factor (78;79). In the Copenhagen Stroke Study we found that for ischemic stroke patients with a history of at least one previous stroke, long term survival was considerably poorer than for patients with a first-ever stroke [figure 1] (78). Other studies disagree that previous stroke influences short- or long-term mortality (12;25;34;43;54). However, it is notable that most of the latter studies included patients from earlier periods, where modern secondary preventive measures such as antihypertensive therapy and antiplatelets were perhaps not fully implemented (12;43), or included a limited number of patients (25;34). Our finding that a former stroke predicts five-year mortality among ischemic stroke patients independent of age, stroke severity, and risk factor profile underlines the importance of secondary preventive strategies to be established after stroke. The prevention of a subsequent stroke is most probably of vital long-term significance for patients with acute ischemic stroke.

Living Alone:

Living status (living alone or with a spouse) is often affected by alterations in people's health condition. Nonetheless, living status at stroke onset can be considered an irreversible factor for epidemiological reasons.

There is a large variation in the frequencies reported by studies for living alone ranging between 23% to 57% (14;20;35;41;43;49;80-83) and those living alone are in general more likely to be women (41;49;82). The probability of living alone before stroke onset increases with age, from between 22.2% and 35.8% for those younger than 65 years, to between 40.0% and 60.4% for those older than 80 years (18;20;81). Among the oldest old (> or = 85 years) in the Copenhagen Stroke Study, 83.5% were living alone (14).

Although many population-based studies have documented living status at stroke onset, only very few have included living status in investigations of stroke survival (12;14;18;20;35;41;43;49;80-85) [table 5]. A minority of these studies do not evaluate stroke survival in relation to living status (20;49;81;82;84). Furthermore, comparisons across studies are very difficult, because of disparities in study design and demographic dissimilarities.

Two studies reported the crude survival after stroke in relation to living status and found no significant influence of living alone versus cohabitation (80;83). Seven studies analyzed the predictive influence of living status at stroke onset for survival after stroke, independent of other prognostic variables (12;14;18;35;41;43;85). Five of those studies reported that living status had no significant independent influence on survival (14;18;35;41;85). While one study found that living alone versus being married increased the relative risk of dying within one year after stroke by 2.2 for ischemic stroke patients (43), another study found that being married carried a worse prognosis for survival (12). It is noteworthy that in the Copenhagen Stroke Study living alone versus cohabitation has previously been reported to raise the risk of delayed admission (> 6 hours from onset to admission) to hospital almost two-fold (OR, 1.75; 95% CI, 1.30 to 2.30) (86). However, that did not seem to have any independent significance for in-hospital mortality (14).

Stroke Characteristics:

Stroke characteristics (anosognosia, hemineglect, apraxia, and aphasia) signify a group of neuropsychological symptoms that very often accompany the cerebrovascular syndromes. The relation to recovery and rehabilitation is most often reported, while the implications for survival are less well known, but these disturbances may nonetheless have significant influence on life expectancy after stroke.

There is no strict consensus about the definition of anosognosia, but in this review the term refers to anosognosia for hemiplegia (i.e. the lack of awareness or the underestimation of a specific neurological deficit). This syndrome was first reported by Babinski in 1914, who was the first to assign a name to this symptom (87). The prevalence of anosognosia for hemiplegia is reported within a wide range between studies and reflects the variation in study design, setting, and time from stroke onset to assessment (88-93). The prevalence is highest (17% to 33%) among patients tested within a few days of stroke onset (88;89;93), and decreases over time to between 10% and 23% during the rehabilitation phase (90-92). The significance of anosognosia for survival has been investigated in two recent studies (89;93) [table 6A]. Appelros et al. found anosognosia for hemiplegia to be significant for 1-year mortality in 272 stroke patients from a community based population, however anosognosia for hemiplegia was not an independent predictor after adjustment for age and stroke severity (93). In the much larger community-based Copenhagen Stroke Study that investigated 566 patients acutely after onset, anosognosia increased the likelihood for death during hospital by a factor of 4.4 after adjustment for onset stroke severity, age, and risk factor profile (89).

There is no firm designation of the term “hemineglect”, but hemineglect is usually understood as the absence of the ability to react to stimuli on the one side of the body that is opposite the brain lesion (94). The incidences reported in early studies of acute stroke ranges from 8% (95) to as high as 82% (88), but has more recently been reported to be between 23% and 43% (93;96-98). The frequency increases with stroke severity (93;97;98), age (97;98), and has a preponderance for right hemispheric strokes (88;93;97;98), although a substantial portion of stroke patients with left hemispheric lesions also seems to have hemineglect as well (88;99). In the Copenhagen Stroke Study short term mortality for patients with neglect versus without was significantly higher (17% versus 6 %) (97). Kalra et al. reported that 6% of 47 patients with hemineglect died during rehabilitation (96), while Appelros et al. reported 1-year survival to be 32% for patients with hemineglect among 272 patients (93). The independent influence of hemineglect after stroke has only been investigated in two studies and neither of these reported any adjusted influence for hemineglect on survival (93;97) [table 6B].

Apraxia is an impairment affecting the purposeful execution of learned and meaningful skills that cannot be explained by primary motor or sensory impairments, or by deficits in motivation, memory or comprehension. Nonetheless there is still no universally accepted taxonomy of apraxia, nor is there a standardized battery for apraxia assessment. Accordingly, the incidence of apraxia after stroke has been reported in between 4% and 55% of patients (100-104). In most cases of apraxia the lesion is located in the left hemisphere (100;102). However, the majority of studies were conducted including only few selected stroke patients (101-103). Two modern studies that included more than 200 patients reported very different frequencies for the prevalence of apraxia after stroke (100;104). One study included 492 patients beyond the acute stage of stroke, from rehabilitation facilities and nursing homes, and found the frequencies for apraxia to be 28% and 37% respectively. A second study from the community based Copenhagen Stroke Study cohort comprised 618 patients assessed very acutely after stroke onset. In this study apraxia was present in 9% of unselected, acute stroke patients. This is significantly lower than is reported in previous studies, and is perhaps best explained by the differences in patient selection, the timing of the testing of apraxia, and the ways of testing apraxia when studies are compared. The implications of apraxia for survival has not been investigated, but it does not influence functional outcome (100).

Aphasia is the loss or impairment of language caused by damage to the brain. It is one of the most devastating impairments after stroke, because the significance of language function for personal identity is crucial (105), recovery is slow, and because it is still present in 61% of aphasic patients one year after symptom onset (106). Aphasia is present in 24% to 38% of acute stroke patients (41;106-109). The frequency of aphasia increases with stroke severity (109), and with age (28;41;109). Furthermore, the severity of aphasia increases with severity of the neurological impairment resulting from stroke (109). In the majority of cases with aphasia after stroke, the lesion is located in the left cerebral hemisphere (103;109;110), but as many as 10% of patients with aphasia has a lesion in the right hemisphere (109). Although, 6 months mortality rates increase from 10% among patients with mild aphasia to 47% among patients with severe aphasia (109), the independent significance of aphasia for mortality after stroke disappears after adjustment for age, severity of stroke, and comorbidity (41;111) [table 6C].

POTENTIALLY MODIFIABLE FACTORS

Stroke Severity:

An important issue is the contribution of stroke severity to survival. Stroke severity, i.e. the amount of neurological deficits, together with age, are perhaps the most consistent and powerful predictors of stroke survival (112;113). Furthermore, stroke severity measured on admission correlates very well with the amount of tissue damage within the brain after stroke. However, despite the numerous studies reporting on stroke survival in relation to stroke severity (12;14;15;19;35-37;39;40;43;53;54;77;79;83;114-119) [table 7], only a very limited number of studies have used validated commonly utilized stroke scales to measure severity on admission (14;35;40;54;114-116). Some studies used the Glasgow Coma Scale to measure stroke severity (36;39;117) others have employed scales suitable for measuring activities of daily living (37;53), neither is validated for the assessment of neurological impairment. Several other studies have exercised estimations of stroke severity based on level of consciousness, amount of leg or arm paresis, and thus created stages of neurological impairment (12;15;19;34;43;77;79;83;118;119). Many studies have investigated the influence on survival within 1 month (short term survival) after stroke onset (14;15;19;34;77;83;115;116;118;119), survival between one month and one year (intermediate term survival) (35;36;39;43;54;77;83;114;115;117-119), and long term survival (> 1 year) after stroke (12;14;36;37;40;53;77;79;83). Despite the fact that all these studies are difficult to compare in terms of the relative impact of severity on survival, all studies collectively reported that severity at the onset of stroke is a strong predictor of survival. The more severe strokes the higher the overall risk of dying after stroke. In the Copenhagen Stroke Study a 10 point decrease of SSS score on admission predicted a more than two-fold (OR, 2.3; 95% CI, 2.0 to 2.6) increase risk for death during hospital stay after adjustment for variations in other prognostic markers (14).

Several methods to alleviate the load of stroke severity have been proposed. These include intravenous thrombolysis for acute ischemic stroke (10), anticoagulation with low molecular weight heparinoids in the acute state of ischemic stroke (120;121), neuroprotective agents (122-124), and hypothermia (125-127).

Today, thrombolytic therapy is the only available medical therapy for acute ischemic stroke that can decrease the severity of stroke and has proven to be efficient (10;128). Despite the fact that thrombolytic therapy has been able to improve functional outcome, the survival rate for patients treated with thrombolysis has not improved, but the treatment is nevertheless recommended for use within three hours from stroke onset in the United States (129). In Europe, final marketing authorization for the thrombolytic agent Actilyse was achieved in 2007 under similar conditions as in the United States, ultimately based on the results of the SITS-MOST surveillance study (130). However, the use of thrombolytic therapy in acute stroke is hampered by two aspects. First, thrombolysis is associated with symptomatic ICH in approximately 5-6% of the treated patients in the United States (131), while a somewhat lower risk is reported from the European SITS-MOST trial (130). Second, from a population-based point of view thrombolysis remains a treatment only for a minority of stroke patients. In a simulation model based on population-based Copenhagen Stroke Study cohort (132) we estimated that 5.3% of the patients would be eligible for thrombolysis after applying the NINDS-rtPA trial criteria (10), and that even fewer (0.4%) would ultimately benefit from this treatment. Although this low proportion of eligible patients may appear rather speculative, similar figures (6.1%) have been found in a large German population of ischemic stroke patients (54), and in another Danish post hoc analysis of thrombolysis in a community-based cohort (133).

Heparin and later low molecular weight heparinoids (LMWH) were used for many years in the treatment of acute ischemic stroke. Nevertheless, no major randomized clinical trials were published before the International Stroke Trial in 1997, which showed no favorable outcome for patients treated with heparin (134). Later LMWHs were tested in at least two major randomized controlled clinical trials, but failed for futility (120;121). While most ischemic strokes are anticipated to result from blood clot formation within cerebral arteries the proposed mechanism behind the action of LMWHs has been a reduction of the ischemic area supplied by the affected arteries. In addition, LMWHs were also thought to reduce the risk for recurrent thromboembolism after initial stroke, deep vein thrombosis, and subsequent pulmonary emboli. However, LMWHs may also increase the risk of devastating intracranial hemorrhage and other major extracranial life threatening bleeding events. In the most important studies there was no proof of the ability of heparin or LMWHs to decrease the severity of stroke among ischemic stroke patients, and hence reduce the overall mortality and/or improve outcome (135). Conversely, the risk of significant bleeding events increased with escalating doses, and the treatment regimen with heparin and heparinoids as a treatment for acute ischemic stroke has been abandoned (129).

Neuroprotective efforts developed as a result of the gradual revelation of the mechanisms underlying the ischemic cascade, as first summarized by Pulsinelli in 1992 (136): Ischemia leads to presynaptic depolarization in the penumbra. This is followed by the release of large amounts of excitotoxic neurotransmitters such as glutamic acid that in turn causes calcium ions to rise steeply within the postsynaptic cells and facilitate production of free radicals. These mechanisms proceed in a cascade-like manner, gradually widening the ischemic zone and subsequently augment neuronal death and inflammation. Several randomized clinical trials have each focused on only one part of this complex system, such as the action of glutamic acid (122), the trapping of free radicals (137), and the destructive action of leukocytes within the penumbra (124). However, all previous trials have failed to pass phase II or phase III clinical trials because of lack of efficacy.

In animal stroke models, neuronal damage is significantly reduced by hypothermia and for this reason hypothermia has been affirmed “the golden standard” of neuroprotection (138-140). In humans hypothermia is established routine during cardiovascular surgical procedures that include cardiac arrest, in order to achieve neuroprotection (141). In stroke patients, low admission body temperature leads to a lower short (142;143) as well as long-term mortality after stroke (40). Moreover, low admission body temperature is an independent predictor of a favorable functional and neurological outcome after discharge (143;144). In the Copenhagen Stroke Study, we therefore conducted a case-control study of applied modest (approximately 35.5 degrees) hypothermia, in which 17 patients underwent cooling therapy for 6 hours with a surface cooling technique (127). The aims of the study were to evaluate the feasibility and safety of this novel approach in treatment of acute stroke. The hypothermia group (cases) was compared with a control group from the community based Copenhagen Stroke Study cohort, matched for admission stroke severity, age, admission body temperature, and sex, because these factors were anticipated to be the primary determi-

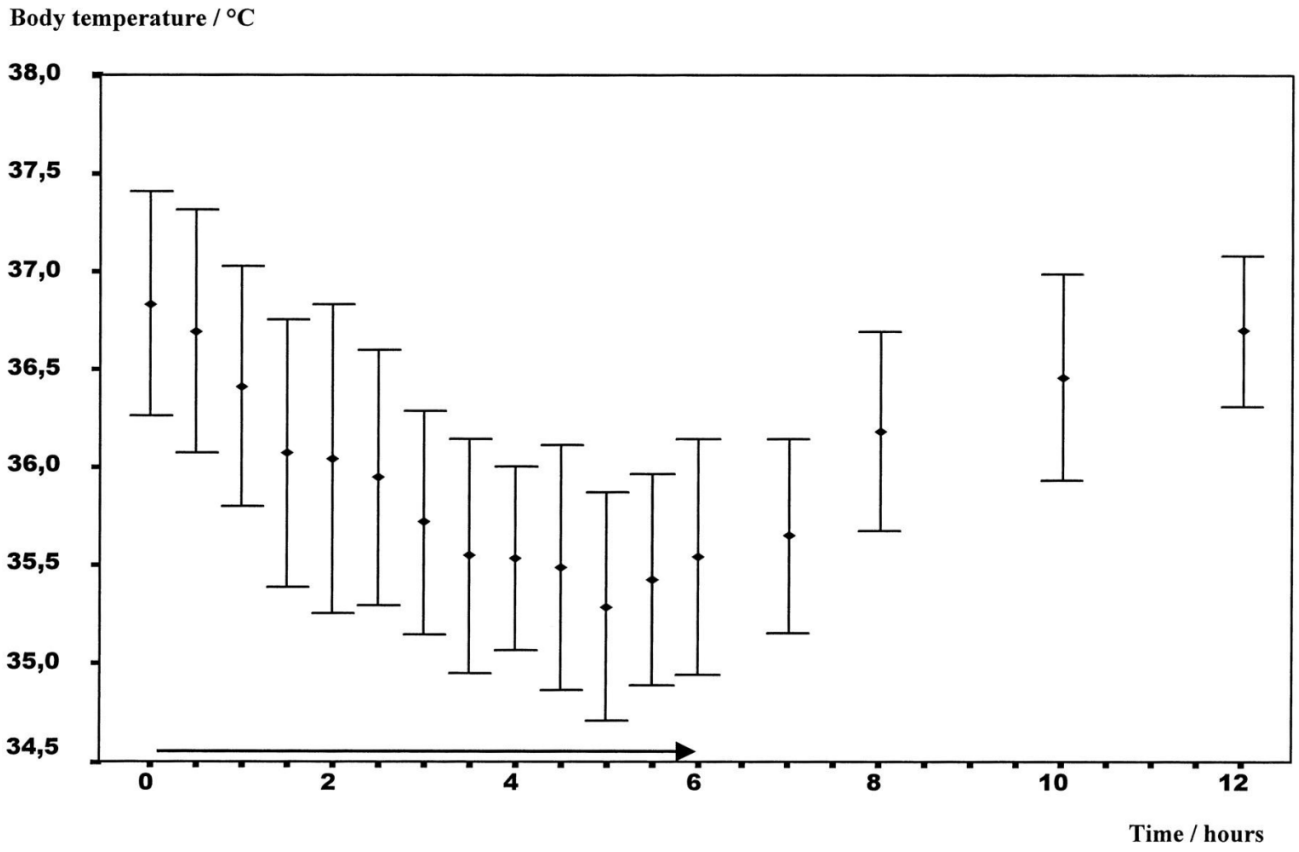

Figure 2
Consecutive measurements of body temperature (tympanic) during and after hypothermic therapy (n=17). Vertical bars indicate standard deviations and arrow indicates duration of hypothermic therapy.

nants of outcome. Figure 2 shows the body temperature during the cooling procedure and the subsequent hours. Patients were followed for 6 months and we concluded that modest hypothermia is feasible and safe. The next step, a randomized controlled trial within the settings outlined in this study, is still pending.
Other studies have used somewhat different approaches to applied hypothermia in acute stroke patients. Schwab et al. showed that moderate hypothermia (approximately 33 degrees) was safe and feasible in 25 patients suffering from malignant middle cerebral artery infarction (126). However, in that study patients were cooled for significantly longer time and required an intensive care unit. In the COOL AID study 40 patients with acute ischemic stroke were randomized to hypothermia versus control, and cooling was performed in patients by an endovascular cooling device (125). Target body temperature (33 degrees) was achieved more rapidly (< 1 hour) than in the former ones. The treatment was well tolerated and the frequencies of side effects were not different. However, no net benefit of treatment was seen with regard to outcome score on NIHSS or lesion growth measured by diffusion weighed images on MRI before and after treatment.
MODIFIABLE FACTORS

Poststroke Infection and Leukocytosis:
Infection after stroke is preventable and treatable, and acute systemic infection may possibly have important implications for stroke outcome and, as a result my have great significance for clinical practice. A number of studies have focused on the frequency of infections, but direct comparisons between these studies are difficult when factors such as study design, setting, selection bias, reporting of post stroke intervals, and definitions of infections are taken into account (145-157). Hence, there is a wide variation in the reported frequencies of infections for the most predominant subtypes; urinary tract infections occur between 1.7% and 30.5% (145-148;150;151;153-162), and pneumonias between 5.6% and 21.6% (145-158;160-163). The highest frequencies of infections were seen among stroke patients in intensive care units (149;163) and among patients from rehabilitation facilities with a lengthy monitoring period (153;155). In the Copenhagen Stroke Study we investigated early infection, within 3 days of admission, among 1,156 patients with acute stroke (151). The most predominant infections were urinary tract infections in 9.9% followed by pneumonias that affected 6.6% of the patients. Urinary tract infection was the most predominant infection in females and occurred almost three times more frequently in women than in men. Men and women had pneumonia with approximately the same frequencies. Both findings are quite similar to that found in another study (156). The factors that predispose to infections after stroke onset are advancing age (147;151;158;160;161), and more severe stroke (147;148;151;152;161;163), consequently clinicians should be aware that these patients are more prone to infections. Females are most frequently affected by infections, especially urinary tract infections (147;151;152;160;161). The adverse effect of infections on survival after stroke has been less well investigated (149;151;152;156;158;160;161) [table 8]. Most studies found that pneumonia was associated with a higher mortality rate

(149;152;161), while another study found that patients with infections irrespective of the type had a higher risk of in-hospital mortality (OR, 2.5; 95% CI, 1.3 to 4.9) relative to patients without (158). In the Copenhagen Stroke Study we found that patients with early infection were less likely to survive hospitalization, however this disadvantage for patients with infections disappeared after adjustment for admission stroke severity, age, gender, and differences in risk factor profile (151). Instead, early infections appeared to prolong hospital stay, a finding that has been confirmed in a later study (156).

The interaction between post stroke infection and the stroke lesion itself appears to be complex. The acute phase response seen in the process of inflammation (i.e. mobilization of leukocytes, CRP etc.) has been reported to be activated during atherogenesis (164), increased in the week preceding a stroke (165), and directly involved in the pathophysiology of the stroke lesion (166). However, apart from infection, the leukocyte count is also affected by other factors such as age, smoking, and diabetes (167). In the Copenhagen Stroke Study leukocytosis (leukocyte count > 9x109 U per liter) was present in 45.3% of 812 patients admitted within 24 hours after stroke onset (168). Leukocytosis was associated with younger age, diabetes, smoking, and fever, but notably not infection within 3 days of hospitalization. There was a strong inverse correlation between leukocyte count and onset stroke severity as measured by the SSS score [figure 3], and a strong positive correlation with infarct size on CT scans in patients with ischemic stroke lesions. However, leukocytosis was not a predictor of in-hospital mortality after adjustment for stroke severity, body temperature, infection, and variations in risk factor profile. Instead, we concluded that leukocyte count is first and foremost an indicator of stroke severity. Christensen and Boysen reported increased white blood cell counts (WBC) within the first 24 hours after stroke onset from those with the most severe strokes, from a group of 719 patients. An unadjusted correlation between WBC and stroke severity on admission, but there was no independent relation between WBC and mortality 1 year after stroke (115). Another study found that leukocyte count was positively correlated with lesion size on CT-scans in 241patients with acute ischemic stroke, and that leukocyte count was related to stroke outcome. However in that study, stroke severity was not measured on admission (169). A Polish study of 400 ischemic stroke patients admitted to hospital within 12 hours afteronset found that WBC predicted higher risk of dying during hospital admission independent of variations in risk factor profile. However, despite the fact that stroke severity was measured on admission, the authors did not adjust for severity of stroke (170).

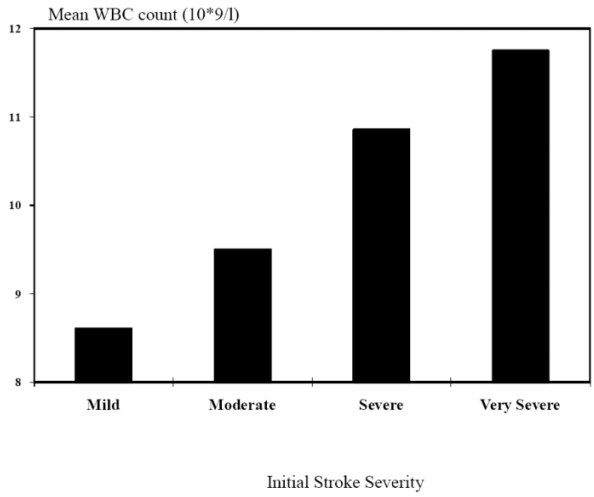

Figure 3
The figure shows mean leukocyte count as a function of Initial Stroke Severity (ISS). Patients were stratified into four subgroups of initial stroke severity according to the initial score on The Scandinavian Stroke Scale (SSS, maximum 58). Mild: 58-44, Moderate: 43-29, Severe: 28-15, Very Severe: 14-0.

Stroke Unit versus General Medical Ward:

Stroke units (SU) are usually defined as wards providing complex organizational intervention comprising multidisciplinary staffing and a complex package of care to stroke patients in hospital (171). However, this definition covers a whole range of designs: Acute SUs with intensive monitoring and early discharge (admission < 7 days), rehabilitation SUs that receive stroke patients after the acute phase (usually 7 days after stroke), and SUs that are more or less a composite of the two designs.

The Copenhagen Stroke Study comprised a cohort of stroke patients admitted acutely to a dedicated SU, where all acute treatment, work-up, and rehabilitation took place. Patients were from a well defined catchment area and no selection was performed with regard to age, comorbidity, premorbid function, or social status. Patients were not discharged before all members of the rehabilitation team (nursing staff, physiotherapists, occupational therapists, speech therapists, and doctors) considered that the patients had achieved maximum recovery (172). We compared short-, intermediate-, and long term mortality between this cohort and a similar group from a neighboring community treated in a general medical ward (GMW) (85). Treatment in SU improved survival in comparison with treatment in GMW. One month case fatality was 17% versus 23%, one- year case fatality 32% versus 39%, and five-year case-fatality was 64% versus 71% for SU and GMW respectively. These findings were consistent after adjustment for variations in risk factor profile. Moreover, we found that treatment in a SU reduced the relative risk for death five years after stroke by 40% in comparison to treatment in a GMW (85). Similar comparisons of survival between SU and GMW have been performed in several other studies (5;173-179) [table 9]. Indredavik et al. reported a randomized trial of allocation to SU versus GMW and found even lower mortality rates six weeks after stroke than in our study (5), but mortality rates five years after stroke were similar to our results, and still in favor of patients treated in SU (180). Indredavik et al. reported a long-term benefit of treatment in SU as long as ten years after stroke onset (181). These results have been confirmed in other studies (174;176-178), but

not all (173;175;179). In the study by Kaste et al. there were no differences in one-year case-fatality rates for patients in SU compared to GMW (175), and in a Swedish study the authors reported a temporary trend in survival in favor of patients from SU, who had concomitant heart disease, although this advantage disappeared three months after onset (173). These findings could suggest that perhaps only a special group of stroke patients will benefit from treatment and rehabilitation in SU. In a community-based study, which included patients from the Copenhagen Stroke Study, we sought to investigate whether the effect of a SU on survival were limited to a certain minority of stroke patients (182). In this study we found that patients treated in a SU had a better survival during hospital stay irrespective of their sex, old age (age > or = 75 years), or they had severe strokes after adjustment for variations in risk factor profile. Furthermore, there was a trend towards a favored survival among patients treated in a SU when we analyzed survival 5 year after stroke onset, but this did not reach statistical significance. Instead the favored survival for severe strokes had disappeared at five years, while patients with mild to moderate strokes now seemed to have a favored survival from rehabilitation in a SU. The reason for that shift in respect to stroke severity might be the higher long-term mortality among patients with the most severe strokes, which limited the statistical power of the study. Nevertheless, we concluded that in terms of survival, all patients seem to benefit from SU treatment irrespective of severity of stroke and sex. Elderly patients, in particular, seem to improve survival more than the younger when treated in a SU. Despite these rather encouraging findings, elderly Danish patients with stroke still today appear to have poorer access to treatment in SUs than younger patients (20).

Cholesterol:

In this paper cholesterol refers to total serum cholesterol and not to subfractions of cholesterol, which is beyond the scope of this paper. The role of cholesterol as a risk factor for stroke is still under debate (183-185), while the status as a risk factor for coronary heart disease CHD is well-established (186;187). Two large meta analyses of several clinical trials found no significant variation for stroke risk between patients with different total serum cholesterol levels (188;189). But the effect of cholesterol on the risk of ischemic stroke might have been diluted, because both analyses included cerebral infarction, intracerebral hemorrhages, and subarachnoid hemorrhages. Hence, it has been suggested that increased cholesterol levels indicate a higher risk only for ischemic strokes (190;191), and lower cholesterol designates a higher risk for cerebral hemorrhages (190). The relation between cholesterol level and survival after stroke is also unsettled. The majority of studies have reported higher serum cholesterol to be associated with lower short- term mortality after stroke (192-194) [table 10], and therefore proposed that cholesterol exerts a neuroprotective effect after stroke (194). However, none of these studies measured stroke severity and therefore did not take the relation between severity of stroke and total serum cholesterol into account. In the prospective Copenhagen Stroke Study, we retrospectively related total serum cholesterol to stroke severity at onset in a 10-year follow up study of 652 patients with acute ischemic stroke (195). We found a positive curvilinear fitted relation between SSS score on admission and total serum cholesterol [figure 4]. Hence, the more severe the stroke the lower the total serum cholesterol, adjusted for the influence of age and risk factor profile. Furthermore, we found the probability of long-term mortality (10 year) after stroke to be inversely related to total serum cholesterol, adjusted for the influence by other predictors of mortality. According to that study each increment in total serum cholesterol resulted in a decreased independent probability (HR, 0.89; 95% CI, 0.82 to 0.97) of survival. These findings suggest that high cholesterol levels are related to mild strokes and that is the reason for the better survival.

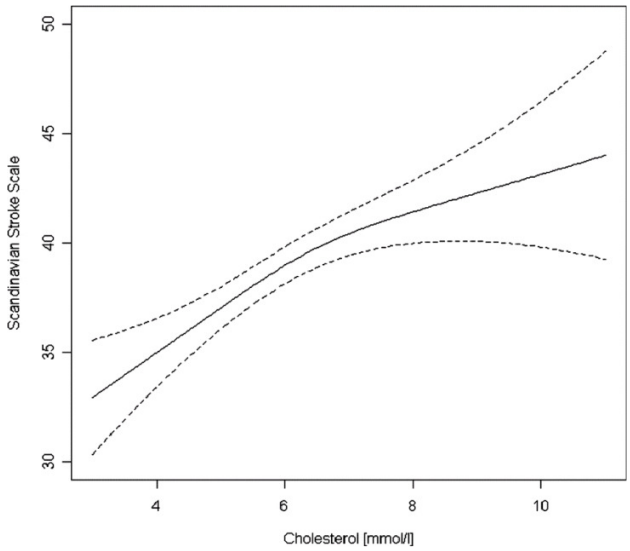

Figure 4
Fitted relation between SSS score and total serum cholesterol levels (solid line). The dotted lines indicate standard errors of the fit.

Atrial Fibrillation:

Non-valvular atrial fibrillation (AF) is a common heart disease in the general population. The prevalence increases with age from less than 1% in people younger than 60 years to 9% among those older than 80 years (196). Hence, AF is primarily a problem in the elderly population and the prevalence is projected to increase along with other cardiovascular risk factors with the ageing population (197). In a North American population-based study of the temporal trends of AF, the relative increase in incidence rates rose more than 10% between 1980 and 2000 (197). The presence of AF is associated with a four to seven times increased risk of ischemic stroke (198;199). The increased propensity for patients with AF for thromboembolism and subsequent ischemic stroke is caused by the concomitant action of left ventricular dysfunction (200), and abnormal stasis in the left atrial appendage (201).
The prevalence of AF in stroke patients is reportedly between 12% and 38%, depending on the selection of the patients included (15;17;21;31;33;35;39;43;48;49;52;114;202-205). In most studies AF appears to be more prevalent among women with stroke (15;48;52;205), but some find there is an equal distribution of AF in men and women (17;39;49). The prevalence of AF in stroke rises steeply with age (28;31;205), and is present in 37.4% of very old stroke patients (> or = 85 years old) compared to the 14.6% seen in younger patients (14). AF is often associated with non-lacunar strokes (31;203), more severe strokes (31;205), and larger lesions on CT (205), which support the hypothesis that ischemic stroke caused by AF is usually of embolic origin. There is a close association between ischemic stroke and AF, thus AF is only present in 2% to 6% of patients with ICH (31;204;205).
The unadjusted death rates during hospital admission are reported to be higher for patients with AF ranging from 19% to 33% for patients with AF versus 12% to 17% for those without

(31;205). In the Copenhagen Stroke Study, it was found that before adjusting for stroke severity, age, and risk factor profile AF was associated with a 1.7 fold raised relative risk of death during hospital stay (205). However, this raised relative risk disappeared after adjustment for admission stroke severity (14;205). This relation has been disputed by four later studies (15;31;116;204) [table 11], which reported AF to be a significant independent predictor of in-hospital mortality, but three of the studies did not use validated measurements for stroke severity (15;31;204), and the fourth did not adjust for stroke severity at all (116). When survival up to one year is considered most studies agree that AF is consistently associated with a poorer survival (21;31;35;43;114) [table 11]. In the study by Lamassa et al. (31) they found AF to be strongly associated with 3-months mortality raising the risk of death by a factor 1.6 relative to patients without AF. A similar relationship between AF and survival has been reported by other studies (21;35;43;114), but not by all (39;203). A Swedish study followed 2,290 patients and found AF to be a significant independent predictor of 3-year mortality raising the relative risk by a factor of 1.4 (37). In the community based Copenhagen Stroke Study, which included unselected stroke patients with both ischemic and hemorrhagic strokes, we followed 1,197 patients for 84 months and found AF to predict a higher probability of death (HR, 1.3; 95% CI, 1.0 to 1.6) after making adjustments for variations in risk factor profile, especially age and stroke severity (14). The Copenhagen stroke study also found 5-year mortality rates for ischemic stroke patients to be 79.4% in AF patients versus 54.6% in those without (78) [figure 5]. Furthermore, AF was an even stronger independent predictor of a higher probability for long term mortality among patients with ischemic strokes than among all stroke patients (HR, 1.4; 95% CI, 1.1 to 1.7). The strong and long-term effect of AF on mortality has also been found by other authors (33;203). Hence, AF tends to be a long lasting risk factor for stroke and continues to add to mortality even a long time after stroke onset.

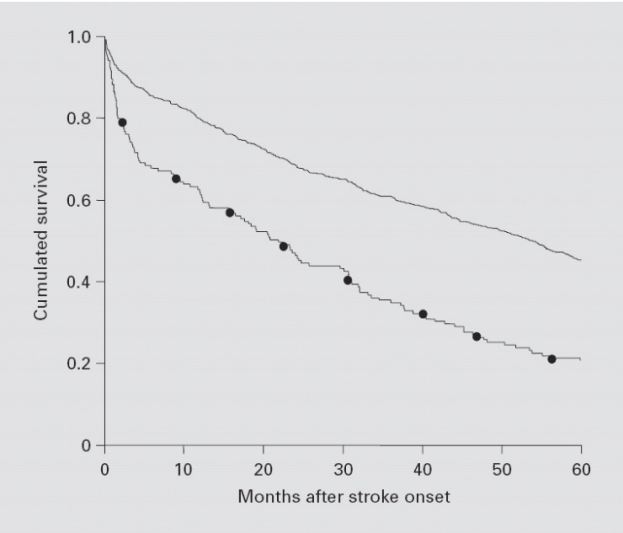

Figure 5
Kaplan-Meier survival plot for patients with ●—● versus without —— atrial fibrillation (n = 890; p < 0.0001).

The risk for patients with AF for thromboembolic complications such as ischemic stroke, lead to the assumption that anticoagulant therapy with vitamin K antagonists could provide protection against the adverse effect of AF. Six randomized, controlled clinical trials have compared warfarin with either placebo or controls for the prevention of stroke in patients with AF (206-211). However, only one trial included a secondary prevention study group (i.e. a group with previous stroke) (211). But in that study, which comprised 225 patients who received anticoagulation with warfarin, patients had TIAs or minor ischemic strokes. Thus, the study is difficult to translate to a clinical setting, because it was significantly hampered by the pre selection of stroke patients. It failed to demonstrate a reduction in all cause mortality for oral anticoagulants (8%) versus placebo (9%), NS. More frequently, meta-analyses have demonstrated that for patients with AF treatment with dose adjusted anticoagulant therapy reduces all cause mortality by 30% compared with placebo, and there is a 60% relative risk reduction for thromboembolic events including ischemic stroke (212;213). ICH is the most feared complication to oral anticoagulation therapy, but is by many clinicians a clearly overestimated risk (214). The annual rate of ICH in clinical trials was less than 1%, whereas the frequency of the entire number of significant bleedings was somewhat higher (between 1% and 2%), and increases with increasing target values of INR (207-211). In the clinical setting, frequencies of major bleedings with anticoagulant therapy are higher, because patients are less rigorously selected. In patients older than 80 years, who are often excluded from clinical trials of AF, the frequencies of major bleeding events seem to be somewhat higher (3% to 4%), yet uncontrolled anticoagulation is a more important predictor of complications than old age as such (215). Apart from old age, factors for bleeding while on oral anticoagulant therapy, have been identified as recent hemorrhage, excess alcohol intake, concomitant use of acetyl salicylic acid and non-steroidal anti-inflammatory drugs, and poorly controlled HA (216-218). Overall, the net benefit of a reduction of the stroke risks with oral anticoagulation for AF exceeds the hazards of major bleeding events (212).

The underuse of oral anticoagulation in AF patients with stroke has been investigated in a large nationwide Danish cohort of stroke patients (219). In this large scale study of 1909 patients with AF, stroke, and no contraindications to oral anticoagulation therapy, only 60.2% received warfarin. Factors that were found significant for keeping away from warfarin were older age, more severe strokes, and having intermittent claudication. Whereas there was a linear relationship between increasing stroke severity and a lower propensity to receive warfarin treatment, there was a striking relationship with age: At the age of 40 years the prevalence of warfarin was 80%, at the age of 70 years still 70% of the patients received warfarin, while after the age of 80 years there was a rapid decline to only 40% among patients aged 90 years. This is a striking finding, because these patients were perceived as being suitable for oral anticoagulant therapy.

Ischemic Heart Disease:

Ischemic heart disease (IHD) increases the risk for ischemic stroke two-fold in comparison with stroke free control subjects (220;221), and cardiovascular risk factors increases 10-year mortality risk three to eight times (222). However, the prevention of IHD is often also used in the primary as well as the secondary prevention of ischemic stroke. Furthermore, the interaction between IHD, AF, HA, and intermittent claudication makes the independent relation for each of these contributors to survival complex to study.

There is a large variation in the frequencies of IHD among patients with acute stroke. The prevalence of IHD from population based studies varies between 10% and 48% (17;33;35;48;76;78;116;204;223). The prevalence of IHD is lowest

among patients with ICH as compared to that seen in patients with BI (204), and lower among female stroke patients than in males (17;48). The relation between IHD and age is less well established, but a large Danish study reported that IHD, measured as prior myocardial infarction, was present in 7.2% of stroke patients aged < or = 65 years, 12.3% of patients aged 66 years to 80 years, and 11.4% of patients older than 80 years. The significance of IHD for survival after stroke has been investigated in a number of studies (33;35;76;78;116;204) [table 12] and most studies reported that IHD increased short- (116;204) as well as long-term (33;76) mortality after adjustment for other prognostic factors, especially age and stroke severity. Two studies, however, found that IHD was insignificant for mortality one and five years after stroke onset, after adjustment for variations in risk factor profile, age, and especially onset stroke severity (35;78). In the Copenhagen Stroke Study we found that 32.2% of the patients with IHD on admission for ischemic stroke were alive five years after onset, in comparison with 45.7% among patients without IHD (78). However, when we adjusted for differences in cardiovascular risk factor profile, age, and stroke severity at the time of onset, we found that IHD had no independent influence on survival. Similar results (i.e. the absent influence of IHD) were reached for 1-year, 5-year, and 10-year survival when both BI and ICH were evaluated together (14;47).

Arterial Hypertension:

Arterial hypertension (AH) is a well established risk factor for stroke and increases the risk for both BI and ICH (220;224). However, when prevalence of AH and the relation to survival is discussed, comparison between studies is significantly hampered for the following reasons: First, the definitions of hypertensive artery disease have changed over time. In the early nineteen-nineties AH was defined as systolic blood pressure exceeding 160 mmHG or diastolic blood pressure above 95 mmHG on repetitive measurements (225). This definition changed in the late nineteen-nineties, however, and AH has since then been considered present if systolic blood pressure goes above 140 mmHG or a diastolic blood pressure exceeds 90 mmHG (226). The time dependent definitions of AH may also have had an influence on the prevalence of AH, because in the Lausanne Stroke Registry and the Hisayama Study, which followed separate cohorts with different definitions of AH, the prevalence of hypertension increased with the more recent definition of AH (227;228). Second, there are considerable variations in selection criteria between the studies, because some are population based (13), some community based (47), while others include patients when the acute state of stroke is over (229).

The prevalence of AH in patients with stroke diverges remarkably between studies (13;17;35;41;48;69;72;78;204;227-230). Most studies used the old definitions of AH (13;17;37;41;48;66;78;204;224;229), two studies used the new definitions of AH (69;231), and two used both definitions for different periods of inclusions (116;228). In community based studies the prevalence of AH has been reported to be between 30% (17) and 69% (204). AH is usually more prevalent in women than in men (13;17;41;48), but some studies found AH to be as frequent in women as in men (47;227). AH seems to be equally prevalent across age groups (20), but less prevalent among the very old stroke patients, which probably reflects a selection of patients free of hypertension reaching advanced age (14). Patients with ICH have been found to be more prone to have pre-existing AH (204), whereas other studies found that patients with AH were as likely to have BI (68;72). In ischemic stroke AH favors the presence of small vessel occlusion over other ischemic stroke subtypes (231), but no study has reported on the relation between AH and severity of the stroke, measured by a validated stroke scale.

Survival after stroke for patients with AH has only been examined in a few population or community-based studies (35;37;41;66;78;116;204;229) [table 13]. In the Framingham cohort, which comprised stroke patients from 1982 the authors found AH to reduce the probability of 5-year survival from 0.85 to 0.51 (66). However, later studies have not been able to confirm this impact of AH on survival after stroke. Most studies find that AH has no significant influence on survival (35;78;116;229), while one study found that AH had significant influence on survival in ICH, but not in BI (204). In the Copenhagen Stroke Study we investigated the prevalence of AH and the significance for long term survival (78). The prevalence of AH according to the older definitions of AH used in that study (225) was 34% of 899 unselected ischemic stroke patients. Five-year case fatality rates were equal for patients with AH (59.1%) in comparison to patients without (56.9%). After adjustment for significant differences with regard to other risk factors and stroke severity, AH did not bring any independent influence on long-term survival after ischemic stroke. Similar results has been seen when both BI and ICH were included in the analyses for 1-year, 5-year, and 10-year survival (14;47). Interestingly, two more recent studies of unselected patients found that treatment for AH was an independent predictor of short (41) and long term (3-year) survival (37), decreasing the probability of death by 20% relative to no treatment.

There are still great uncertainties about the acute phase of stroke and antihypertensive treatment. Higher blood pressure measurements are often found in the acute state of stroke (232), but whether or not it is feasible to lower blood pressure very early after onset remains disputable. Aggressive treatment with blood pressure lowering drugs may lead to neurological worsening through a reduction in perfusion pressure to hypoperfused areas of the brain (233). In the majority of patients blood pressure declines spontaneously within the first few days after onset (234). However there are several questions that remain unanswered. Should antihypertensives prescribed prior to stroke be discontinued during the acute phase? Which types of antihypertensives are most appropriate after stroke? When should new antihypertensive therapy be allowed to begin? Future randomized clinical trials will further clarify these issues.

Diabetes:

Patients with diabetes mellitus (DM), especially DM type II, have an increased susceptibility to generalized atherosclerosis and often a clustering of other cardiovascular risk factors, such as hypertension, obesity, and increased levels of serum lipids (235). In Europe the prevalence of DM type I in the general population is projected to have reached a steady state, while a further dramatic increase in the prevalence of type II is expected in the years to come (236). The majority of published data linking diabetes and cerebrovascular disease relate to patients with Type II diabetes. In developed countries the reported prevalence in the general population ranges between 1% and 15%, and Scandinavia is among the high risk areas (237). Patients with DM have an increased risk of ischemic stroke with at least a two to four-fold raised relative risk compared to DM free people (238). An estimated 16% of stroke deaths in men and estimated 33% in women are contributed by DM (239;240).

The prevalence of DM in patients with stroke is considerably higher, between 13% and 31.5%

(15;17;21;35;78;79;114;116;161;228-230;241). There was a clear tendency for the prevalence of DM to increase over time in population-based studies, from the late nineteen-seventies to the late nineteen-nineties (228;241). DM was more prevalent among patients with ischemic strokes (17% to 31%) as compared to ICH (10% to 12%) (79;229). In ischemic stroke patients DM is more often associated with small vessel disease (15) and lacunar infarctions (242). Female stroke patients had DM more often than male stroke patients in one study (15), whereas the opposite was found in another (17), and two further studies reported no sex specific differences (41;47). There does not appear to be differences in the prevalence of DM across age groups for stroke patients (20), on the other hand DM is significantly less prevalent among stroke patients older than 80 years old (14;30).. It is recommended to employ tight blood glucose control in both patients with and without DM in the early phase after stroke onset (14;129). Hyperglycemia appears to have a detrimental effect in the acute setting by expanding the stroke lesion (243), augment anaerobic metabolism in the penumbra (244), and cause subsequent clinical deterioration (232;243). However, the evidence for the significance of DM for survival after stroke remains disputable. Some studies report that stroke patients with DM are as likely to survive up to one year after stroke when compared to DM free stroke patients (21;35;41;114;116) [table 14]. A large German study found that DM only reduces the probability of survival until discharge among male stroke patients (15). All studies on long-term survival after stroke report that DM increases the risk for dying after stroke independent of risk factor profile, age, and stroke severity at onset (37;78;79;229) [table 14]. The discrepancy between the studies of the reported influence of DM on survival probably reflects differences in designs and patients included. Hence, one study included patients with BI, ICH, and SAH (37), while others included BI and ICH patients (35;79;114), and the minority of studies included patients with BI only (78). In the Copenhagen Stroke Study we investigated several cardiovascular risk factors including DM in 899 unselected patients with acute ischemic stroke (78). In that study we found patients with DM to have a poorer 5-year survival than those without; 67.2% versus 55.9% respectively [figure 6]. In addition, diabetes was associated with a poorer survival (OR, 1.3; 95% CI, 1.0 to 1.6) when other cardiovascular risk factors, stroke severity, and age were accounted for. In another study that included both BI and ICH we found that DM was also an independent predictor of death at 1-year (OR, 2.09; 95% CI, 1.46 to 2.98), 5-year (OR, 1.44; 95% CI, 1.15 to 1.80), and 10-year (OR, 1.43; 95% CI, 1.18 to 1.73) after stroke when the aforementioned adjustments were performed (47). This indicates that DM most probably is a long lasting risk factor for death after stroke irrespective of stroke type. Studies are warranted to investigate whether stroke patients with DM could perhaps benefit from a regimen with long-term targeted, intensified, multifactorial intervention for secondary prevention after stroke. This has shown efficacy in preventing cardiovascular events in stroke free patients with type II diabetes mellitus (245).

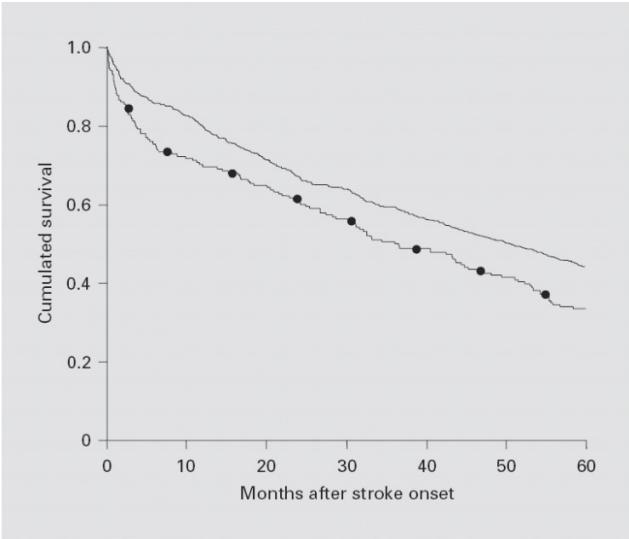

Figure 6
Kaplan-Meier survival plot for patients with ●—●versus without —— diabetes (n = 880; p = 0.003).

Intermittent Claudication:
Intermittent claudication (IC) is a symptom of peripheral arterial disease (PAD). PAD is part of a global vascular problem of diffuse atherosclerosis (246). The classification of PAD comes in three steps: 1) Asymptomatic PAD, which is suspected if lower extremity pulses are missing, and is verified if the ankle-brachial index < 0.9. 2) Intermittent claudication which is defined as discomfort in the calf muscles with exertion and that the symptom subsequently resolves after a few minutes rest. 3) Acute and chronic limb ischemia in the lower extremities at rest (247). In the following section the term IC refers to symptomatic PAD (i.e. step 2 and 3), because ankle-brachial index is usually not performed in the routine clinical stroke setting or in clinical trials of stroke.
The prevalence of PAD among people aged 60 years or more is 12% and rises steeply with age to approximately 29% for the oldest old (248). The prevalence of IC (symptomatic PAD) is somewhat lower, between 2% to 5% among people aged 60 or older (246). One study has reported from a geriatric clinic that if ischemic stroke is present, IC is also present in 28% of the population (249). IC is also two to three times more prevalent among patients with stroke when compared with stroke free controls (74). Nonetheless, few studies have reported on the prevalence of IC in stroke patients, but the prevalence seems to be between 8% and 20% (11;43;48;74;78;116). A recent nation-wide Danish study, however, found an even lower prevalence of 4.4% among almost 30,000 stroke patients (20). According to two studies the prevalence appears to be age dependent, with frequencies increasing with age in patients younger than 80 years old and a subsequent tendency to decline thereafter (14;20). IC is twice as common in men (8.9%) as compared to women (5.4%) with stroke (48). These prevalences for men and women with stroke are almost twice that seen in the general population (246). Intermittent claudication may add to the short as well as the long-term risk for death after stroke. IC is a strong and independent predictor of in-hospital and 28-day case fatality for ischemic stroke patients raising the risk more than two-fold (116;250) [table 15]. However, the influence by IC on mortality beyond the first month after stroke remains disputable. Four studies found that IC had no

independent predictive impact (35;78;79;203), while two papers from the same study group found that IC was a predictor of increased case fatality one year (43) and five years (11) after stroke independent of variations in age and risk factor profile. In the latter two studies severity of stroke was not accounted for by a validated stroke scale. Instead, estimations of stroke severity were measured by level of consciousness (mild, moderate, and severe). In the Copenhagen Stroke Study we analyzed the relation between long-term survival and IC together with other cardiovascular risk factors in 899 patients with ischemic strokes, of which 14.3% had IC (78). Five years after stroke onset a similar proportion of patients with IC (59.8%) as without IC (56.2%) had died. After adjustment for variances of other risk factors, age, and stroke severity measured by a validated stroke scale, IC did not predict long-term mortality after ischemic stroke. This relation has been confirmed by another Swedish study, which employed the NIHSS for measuring stroke severity at onset (35). Thus, IC is more prevalent among patients with stroke than in the general population, and probably indicates a higher risk for mortality among stroke patients. More studies dedicated to investigating PAD in stroke patients are needed. The secondary prevention in patients with PAD (i.e. smoking cessation, antiplatelets, lipid lowering medication, and antihypertensive medication) is quite similar to secondary prevention after ischemic stroke (246).

Smoking:

Smoking causes 4 to 5 million premature deaths worldwide each year and the leading causes of death from smoking are cardiovascular diseases in approximately 1.7 million people (251). Smoking is beyond any doubt a well-known independent risk factor for stroke (252;253) and contributes to a higher likelihood of stroke related deaths (254). The estimated risk for stroke among smokers is raised between 2- and 5-fold in comparison to non-smokers after adjustment for other risk factors (74;220;221;255;256). The prevalence of smoking among patients with stroke is estimated to be from 20% to almost 50% (35;78;115;116;228;230;231). The highest prevalence for smoking among stroke patients was seen in early studies from the nineteen-eighties with a clear trend towards a decline of smoking during the following decades (228;257). This parallels the decline of smoking prevalence in population-based studies (227;241). Smoking prevalence among stroke patients decreases with age (20;258) and was only 18% among stroke patients aged 85 years or more in the Copenhagen Stroke Study compared to a frequency of 50% among the younger patients (14). This relation most probably reflects that stroke patients who smoke are less likely to reach advanced ages. Female stroke patients were less likely to smoke than males in the Copenhagen Stroke Study (47), which is consistent with what is seen in other stroke populations (48;227;258;259).

The impact of smoking on survival after stroke appears to be complex. Most studies agree that smoking among patients with stroke does not have an independent predictive impact on mortality following stroke (11;35;43;116;203;258) [table 16], but this is not universally accepted (37;78). Patients with ischemic stroke who are smokers seem to be more likely to have lacunar strokes and large artery disease rather than cardioembolic strokes (203;230;231). Thus, stroke severity together with other possible prognostic variables, including age, must be taken into account when calculating the adjusted influence of smoking on survival after stroke. Furthermore, recent or current smoking among patients with ischemic stroke in one study found less AF and diabetes (258). This finding may well indicate that the effect of smoking among stroke patients may be counterbalanced by other prognostic factors. In the Copenhagen Stroke Study we analyzed the combined influence of smoking and other cardiovascular risk factors, and their independent impact on survival after ischemic stroke (78). Interestingly, at a first glance the crude all-cause five-year mortality rate for smokers was lower than for non-smokers, at 54.3% versus 59.2% [figure 7]. However, when stroke severity, age, and variations in cardiovascular risk factor profile were adjusted for, smoking was independently associated with a poorer long-term survival than that seen among non-smokers (OR, 1.2; 95% CI, 1.0 to 1.4). The results from this study emphasize the benefit of smoking cessation for life expectancy after stroke. In the Framingham study, ex-smokers had significantly lower stroke risk two years after cessation, and five years after cessation the risk was similar to patients who had never smoked (260). Hence, smoking cessation not only reduces stroke risk, but might also be a powerful tool to improve survival after stroke.

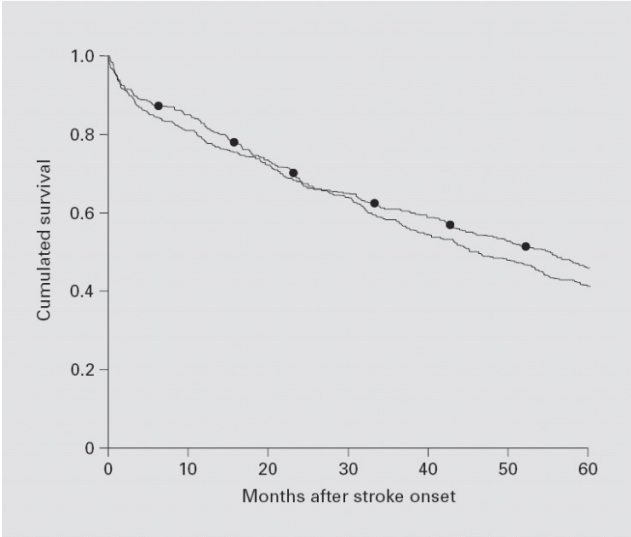

Figure 7
Kaplan-Meier survival plot for smokers ●—● versus non-smokers ——— , (n = 793; p = 0.01).

Alcohol Consumption:

Alcohol abuse can lead to a number of medical complications, including stroke. However, the relation between the stroke risk and the number of alcoholic beverages is not straight forward. A meta-analysis based on 35 observational studies established a J-shaped relationship between the amounts of drinks per day (1 drink equals 12 g of alcohol) and the risk of ischemic stroke (261). Thus, a decreased relative risk was found among people with an intake of one or two drinks per day (light to moderate consumers) when compared to abstainers, while the relative risk of ischemic stroke increased for subjects with a daily alcohol consumption exceeding five drinks per day. In contrast, the relation between alcohol consumption and the relative risk for hemorrhagic stroke increases linearly with the number of drinks per day without any benefit relative to abstainers (261). A number of plausible explanations have been suggested to contribute to this disparity between alcohol consumption and the risk for BI and ICH respectively. Moderate alcohol consumption increases high-density lipoprotein cholesterol levels, inhibits platelet aggregation, and fibrinolytic activity (262). Furthermore, alcohol induced hypertension and impaired coagulation are probably the underlying

mechanisms behind the increased propensity for hemorrhagic strokes among heavy drinkers (263;264).
As for alcohol consumption and survival after stroke the number of studies is very scant (39;76;78;114;257;265). Furthermore, the existing evidence is hampered by diverging definitions of the term "alcohol consumption". Some studies define alcohol consumption as the intake of alcohol on a regular basis (76;78). Others set up a certain limit of alcohol intake (39;265), while the remainder of studies used the term "alcohol abuse" without any definitions of the term "abuse". Finally, only a few studies took into account stroke severity at onset measured by a validated scale suitable for determining stroke severity, before calculating survival as a function of alcohol consumption (78;114).
Most studies, however, found that alcohol consumption had no significance for survival during hospital stay (257) or within 1 year after stroke (39;114), while one large study found that a daily intake of alcohol increased case-fatality 3 months after stroke onset, independent of differences in risk factor profile (265). Two studies with a lengthy follow-up found that regular alcohol consumption did not per se influence survival (76;78). Further studies with more rigorous definitions of alcohol consumption are necessary to explore if there is a dose-response relationship between alcohol consumption and survival after stroke.

Oral Antiplatelet Agents:
Aspirin (ASA) as an antiplatelet agent for preventing ischemic stroke and myocardial infarction was introduced in 1978 (266). Dipyridamole was added in 1987 (267), and clopidogrel in 1996 (268). ASA produces a small but real reduction of about 10 deaths or recurrent strokes per 1000 treated patients during the first few weeks after onset of treatment following an ischemic stroke (134). ASA alone reduces the risk for death and recurrent stroke by 13% in comparison to placebo, and adding extended release dipyridamole reduces the risk by 24% (7). Notably, the latter treatment has no statistical significant effect on the death rate alone (7;269), which could be explained by the relatively higher risk of bleeding vents especially among patients treated with ASA (7). However, the absolute benefits substantially outweigh the absolute risks of fatal bleedings (270). Clopidogrel alone reduces the annual risk of ischemic stroke, myocardial infarction, or vascular death by 8.7% relative to ASA in monotherapy (268). However, the cohort studied comprised a composite of patients with a variety of atherosclerotic vascular diseases that qualified them for the study, and not just patients with ischemic stroke. In the subgroup of patients with ischemic stroke as the qualifying event for entry into the study, no superior effect was found for clopidogrel over ASA in preventing a subsequent stroke, myocardial infarction, or vascular death (268). The combined treatment of ASA plus clopidogrel seems to be associated with increased risk of both minor and major bleeding episodes compared to treatment with clopidogrel alone in unselected patients with a variety of atherosclerotic vascular diseases including ischemic stroke (271;272). The results from the PRoFESS trial of ASA plus extended-release-dipyridamol versus clopidogrel in monotherapy for secondary prevention after stroke have recently been published (273). In that study neither the secondary outcome, a composite of vascular events (stroke, AMI, or death from vascular causes), or the tertiary outcome (death from any cause) showed any benefit for any of the treatment regimens. Taken as a whole, none of the antiplatelet regimens used today produces a reduction in overall mortality after stroke, which has lead to the assumption that a ceiling effect might exist, beyond which adverse effects offset any beneficial efficacy (274).

CONCLUSION
Survival after stroke appears to depend on several factors. Some are risk factors for stroke while others are clinical characteristics that can be identified immediately upon admission to hospital. Some factors are impossible to change, while others are reversible, or possible to modify in order to alleviate the burden of stroke and subsequently improve survival. Knowledge of factors that are significant for the survival after stroke is mandatory when planning acute stroke care and rehabilitation. Furthermore, this knowledge provides pivotal information when informing patients and relatives about the prognosis after stroke. The present findings from the Copenhagen Stroke Study provide new insight into determinants of survival in the short- as well as the long-term.
The two most prominent factors that determine survival are age and stroke severity. Age is perceptibly negatively correlated to survival, even after adjustment for the increased burden of risk factors and other disease that comes with age. Advancing age is an independent predictor of both short- and long-term survival after stroke. Survival after stroke is negatively correlated to stroke severity. In the Copenhagen Stroke Study, which is the only population-based study with a lengthy follow-up that has measured onset stroke severity by a validated stroke scale, we found that stroke severity determines post stroke survival even several years after onset. This emphasizes the need to measure stroke severity with scales suitable for the assessment of stroke patients when conducting clinical stroke trials and monitoring clinical treatment regimens. Recent advances in the treatment of stroke patients have been aimed towards decreasing the severity of stroke by the introduction of thrombolytic therapy for acute ischemic stroke for early clot lysis. Future strategies to alleviate severity in stroke patients might include treatment with hypothermia and other neuroprotective measures.
Reports on the significance for survival of being a female or male stroke patient have diverging conclusions. Most studies find that sex has no influence on mortality, while a few studies find that either women or men have a better survival. Recently, a large Danish study suggested that survival for women is better in the short-term and long-term perspective, while intermediate survival is equal for men and women. Whether or not sex-related biological differences are the true explanation for this new finding remains to be elucidated.
The role of several risk factors in predicting survival remains disputed. Studies disagree when factors such as a history of previous stroke, ischemic heart disease, arterial hypertension, and intermittent claudication are considered. Conclusions from studies of survival in relation to life style related factors such as smoking and alcohol consumption are weak because of diverging definitions of the intensity of exposure to these factors. Furthermore, a risk factor such as smoking is more frequently present in younger stroke patients, and since younger patients are expected to live longer than older patients this leads to a higher crude survival rate for smokers. However, by adjusting for other factors such as age, smoking is associated with a poorer survival. Diabetes is in most studies not associated with a poorer short-term survival. On the other hand, stroke patients with diabetes have a higher probability of death years after stroke onset irrespective of treatment. The significance of this finding is yet to be explored, but future improvements in the treatment of diabetes could be a valuable therapeutic tool for improving long-term stroke survival.
The relation between total serum cholesterol and survival after stroke appears multifaceted. High total serum cholesterol is associated with milder strokes, which probably explains why choles-

terol level is also associated with increased survival after ischemic stroke. On the other hand, low serum cholesterol levels seems to be associated with intracerebral hemorrhage, which is often associated with higher mortality rates. Treatment with lipid lowering agents such as statins for secondary prevention after stroke decreases the risk for recurrent cardiovascular events, but does not improve crude mortality rates after stroke.

Treatment in a stroke unit versus in a general medical ward is a well established measure to improve short- as well as long-term survival. Although early reports suggested no effect of stroke unit treatment on survival, later studies have proven that survival for patients randomly assigned to stroke units versus general medical wards is better even several years after stroke. Furthermore, stroke unit treatment improves survival for all patients regardless of age, stroke severity, and risk factor profile. Little is known about how stroke units improve survival, but the combined effort by dedicated staff and therapists may help to prevent the occurrence of medical complications such as infections and fever that may affect mortality. The further implementation of stroke unit treatment is a powerful tool to improve survival after stroke.

Patients with intracerebral hemorrhage are most often considered to have a worse prognosis than ischemic stroke patients. On the other hand, strokes among patients with intracerebral hemorrhages are in general more severe than ischemic strokes. Thus, the increased crude mortality found in most studies could, at least in part, be explained by these variations. In the Copenhagen Stroke Study the two types of stroke, intracerebral hemorrhage and ischemic stroke, had similar survival rates in the short-term as well as in the long-term after adjustment for a number of other prognostic variables including stroke severity.

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