POSTSTROKE SURVIVAL AND ISCHEMIC STROKE RECURRENCE: THE CEREBRAL SMALL-VESSEL DISEASE PERSPECTIVE

Susanna Melkas

ACADEMIC DISSERTATION

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by the roman numerals.


Publication II was also included in the thesis of Niku Oksala (Genetic, Neuropsychological and Neuroradiological Determinants of Survival After Ischemic Stroke, University of Tampere 2009). The publications are reproduced with the permission of the copyright holders.
ABBREVIATIONS

ADL Activities of daily living
AF Atrial fibrillation
AUC Area under curve
CAA Cerebral amyloid angiopathy
CADASIL Cerebral autosomal dominant arteriopathy with subcortical ischemic strokes and leukoencephalopathy
CE Cardioembolic stroke
CHADS2 The Congestive heart failure, Hypertension, Age, Diabetes, Stroke -score for atrial fibrillation stroke risk
CHD Coronary heart disease
CI 95% confidence interval
CIND Cognitive impairment no dementia
CT Computed tomography
CVD Cerebro-vascular disease
DES Depression-executive dysfunction syndrome
DSM Diagnostic and Statistical Manual of Mental Disorders
eGFR Estimated glomerular filtration rate
FRS Framingham Risk Score
HADS Hospital Anxiety and Depression scale
HR Hazard ratio
FLAIR T2-weighted and fluid-attenuated inversion recovery images
IADL Instrumental activities of daily living
ICD International Statistical Classification of Diseases and Related Health Problems
IQCODE International Questionnaire on Cognitive Decline in the Elderly
LAA Large-artery atherosclerotic stroke
LADIS The Leukoaraiosis and Disability in the Elderly study
MMSE Mini Mental Status Examination
MRI Magnetic resonance imaging
mRS Modified Rankin Score
NIHSS National Institute of Health Stroke Scale
NINDS National Institute of Neurological Disorders and Stroke
OCSP Oxfordshire Community Stroke Project criteria
OR Odds ratio
PROGRESS Perindopril Protection Against Recurrent Stroke Study
<table>
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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ROC</td>
<td>Receiver operating characteristic</td>
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<tr>
<td>RR</td>
<td>Relative risk</td>
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<tr>
<td>SAM</td>
<td>The Helsinki Stroke Aging Memory study</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
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<tr>
<td>SPS3</td>
<td>Secondary Prevention of Small Subcortical Strokes study</td>
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<tr>
<td>SVD</td>
<td>Small-vessel disease</td>
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<tr>
<td>SWI</td>
<td>Susceptibility weighted imaging</td>
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<tr>
<td>TIA</td>
<td>Transient ischemic attack</td>
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<tr>
<td>TOAST</td>
<td>Trial of Org 10172 in Acute Stroke Treatment</td>
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<tr>
<td>WM</td>
<td>White matter</td>
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<td>WMC</td>
<td>White matter changes</td>
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The core imaging features of small-vessel disease (SVD) are confluent and extensive white matter changes (WMC) and lacunar infarcts. These are associated with minor motor deficits but a major negative influence on cognition, mood, and functioning in daily life, resulting from small-vessel lesions in the fronto-subcortical brain network. The aim of the present study was to investigate the influence of different manifestations of cerebral SVD on poststroke survival and ischemic stroke recurrence in long-term follow-up.

These sub-studies were conducted as part of the Helsinki Stroke Aging Memory (SAM) study. The SAM cohort consisted of 486 consecutive patients aged 55 to 85 years who were admitted to Helsinki University Central Hospital with acute ischemic stroke. The study included comprehensive clinical, neuropsychological, psychiatric and radiological assessment three months poststroke. The patients were followed up for 12 years using extensive national registers. The effect of different manifestations of cerebral SVD on poststroke survival and stroke recurrence was analyzed controlling for factors such as age, education, and cardiovascular risk factors.

Poststroke dementia and cognitive impairment relate to poor long-term survival. In particular, deficits in executive functions as well as visuospatial and constructional abilities predict poor outcome. The predictive value of cognitive deficits is further underlined by the finding that depression-executive dysfunction syndrome (DES), but not depression in itself, is associated with poor poststroke survival. Delirium is not independently associated with increased risk for long-term poststroke mortality, although it is associated with poststroke dementia.

Furthermore, acute index stroke attributable to SVD is associated with poorer long-term survival and a higher risk for cardiac death than other stroke subtypes. Severe WMC, a surrogate of SVD, is independently related to an increased risk of stroke recurrence at five years.

In summary, cognitive poststroke outcomes reflecting changes in the executive network brain, and the presence of cerebral SVD are important determinants of poststroke mortality and ischemic stroke recurrence, regardless of whether SVD is the cause of the index stroke or a condition concurrent to some other etiology. Focus on large-vessel disease, major stroke, has hampered understanding of the vascular disease and burden of the executive network brain, namely SVD.
TIIVISTELMÄ


Pienten suonten taudin aikaisemman aivovalvauksen jälkeen kuolleisuusriski ja erityisesti sydänperäisen kuoleman riski on suurempi kuin muusta syystä aiheutuneen aivovalvauksen jälkeen pitkääikaissairannasssa. Laaja-alaisten valkean aineen muutosten ennustaminen ennustaa lisääntynyttä aivovalvauksen uusiutumisen riskiä viiden vuoden seurannassa.

Yhteenvetona aivovalvauksen kognitiiviset seuraukset, jotka ovat merkkinä muutoksesta toiminnanahojauksen verkostossa, sekä pienten suonten taudin ilmeneminen ovat tärkeitä tekijöitä kuolleisuudessa ja aivovalvauksen uusiutumisessa. Pienten suonten taudin sitten aivovalvauksen syynä tai muusta syystä aiheutuneen aivovalvauksen rinnakkaisairauksissa. Huomion keskittyminen suurten suonten tautiin on ollut rajoitteena pienten suonten tautia eli toiminnanahojauksesta vastaavien verkostoavojen sairautta koskevan tiedon karttumiselle.
An increasing number of people are living as stroke survivors, even though the age-adjusted incidence of stroke is declining in high-income countries (Feigin et al. 2009). An important reason for this is the decreasing poststroke mortality due to improved acute care including thrombolysis (The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group 1995, Lees et al. 2010) and stroke units (Stroke Unit Trialists’ Collaboration 2007, Meretoja et al. 2010a), and due to improved treatment of vascular risk factors and aggravating factors such as hypertension, atrial fibrillation, cardiac failure, hyperlipidemia and diabetes (Wolf et al. 1991, Dennis et al. 1993, Sivenius et al. 2004, Hu et al. 2005, Rothwell et al. 2005, Tobias et al. 2007).

The proportion of the elderly population is rapidly increasing in high-income countries (Anderson et al. 2000, Schulz et al. 2004), which in turn is expected to increase the prevalence of poststroke cases since stroke risk increases with advancing age. However, according to a recent modeling, the estimate of new first stroke cases in Finland is strongly dependent on the success of risk factor modification (Sivenius et al. 2009). As the annual number of new first strokes (including hemorrhagic) was 10,500 in 2000, the number would remain practically unchanged by 2030 if the present declining incidence trends are maintained, but would double if the favorable trends plateaued.

According to a nationwide stroke database, the mean annual number of incident stroke patients treated in Finnish hospitals in 1999−2007 was 10,480, 79% of whom suffered an ischemic stroke, 14% intracerebral hemorrhage and 7% subarachnoidal hemorrhage as their incident stroke (Meretoja et al. 2010b). Of these patients 27% died and 13% had a recurrent stroke within the first year of their incident stroke. The Finnish stroke prevalence in 2008 was 82,000, or 1.5% of the national population (Meretoja et al. 2010b).

Ischemic stroke generally accounts for 80%−85% of all strokes (Feigin et al. 2009), and approximately 25% of all ischemic strokes are caused by cerebral small-vessel disease (SVD; Norrving 2003). Signs of cerebral SVD are often present also in patients with other subtypes of ischemic stroke, i.e. in strokes due to large-artery atherosclerosis, cardioembolism and other causes (Streifler et al. 2002, Vermeer et al. 2003a). Cerebral SVD also predisposes to intracerebral hemorrhages at both the basal-ganglionic and lobar sites (Labovitz and Sacco 2001, Inzitari 2003).

The core imaging features of cerebral SVD are white matter changes (WMC) and lacunar infarcts (clinically overt or silent), along with enlarged perivascular spaces and microscopic or macroscopic cerebral bleeds (Román et al. 2002, Pantoni 2010, Potter and Román 2011). SVD of the long perforating arteries irrigating the deep
white matter areas mainly in centrum semiovale leads to ischemic WMC and small, often silent lacunes. This first type of SVD seems to be due to arteriolosclerosis and lipohyalinosis (Wardlaw 2005). The second type of SVD appears to be mainly atherosclerotic and affects the deep perforating arteries irrigating the deep gray and white matter in the internal capsule, the basal ganglia, the brainstem, and the cerebellum, leading to large and mostly symptomatic lacunes. Lacunar stroke syndromes have been previously associated with better short-term prognosis than other subtypes of stroke (Anderson et al. 1994, Grau et al. 2001, Kolominsky-Rabas et al. 2001).

WMC and lacunar infarcts are associated with a negative influence on cognition, mood and functioning in daily life (Norrving 2003, Inzitari et al. 2009, Pantoni 2010). Infarcts and white matter lesions affecting the fronto-subcortical circuits have been shown to relate to cognitive decline in stroke patients (Vataja et al. 2003), although other studies have found cognitive influence to occur regardless of the location of the WMC and lacunes (Tullberg et al. 2004, Jokinen et al. 2011).

Subtle changes in cognition are typical of cerebral SVD (Norrving 2008a, Jokinen et al. 2009a), in addition to acute focal neurological deficits. Neuroradiological markers are often already detectable during the silent period of cerebral SVD. In many cases, brain lesions are probably accompanied by other end-organ manifestations indicating that SVD has a systemic nature, and that the brain is one of the SVD end-organs along with the heart, the kidneys, the musculature and the retina (Oksala et al. 2010).

Irrespective of the subtype of index stroke, the presence of SVD should be considered as an important prognostic factor in the long-term perspective. The different manifestations of SVD, as well as their influence on poststroke survival and stroke recurrence demand more attention to ensure the recognition of the warning signs and to develop strategies for secondary prevention, specific treatments, and rehabilitation. Such strategies are needed to improve outcome and avoid expensive adverse outcomes.
2 REVIEW OF THE LITERATURE

2.1 ASPECTS ON CEREBRAL SMALL-VESSSEL DISEASE

2.1.1 PATHOGENESIS OF CEREBRAL SMALL-VESSSEL DISEASE

Cerebral arterial small-vessel disease has two principal forms (Lammie and Wardlaw 1999, Erkinjuntti et al. 2000, Román et al. 2002, Pantoni 2010). Firstly, SVD of the long perforating arteries irrigating the deep white matter areas mainly in the centrum semiovale leads to ischemic WMC and small, often silent lacunes. The second type of SVD affects the deep perforating arteries irrigating the deep gray and white matter in the internal capsule, the basal ganglia, the brainstem and the cerebellum, which together have been entitled the vascular centrencephalon (Erkinjuntti et al. 1994). This second type of SVD leads to large, mostly symptomatic lacunes (Wardlaw et al. 2001).

The etiology of SVD is heterogeneous, probably multifactorial and not completely known (Erkinjuntti et al. 2000, Román et al. 2002, O’Brien et al. 2003, Pantoni 2010). SVD of the long perforators seems to be mainly caused by arteriolosclerosis and lipohyalinosis, whereas SVD of the deep perforators appears mainly atherosclerotic (Wardlaw et al. 2001). Cerebral amyloid angiopathy (CAA) and cerebral autosomal dominant arteriopathy with subcortical ischemic strokes and leukoencephalopathy (CADASIL) are non-inflammatory arteriopathies causing SVD, the latter being a distinct genetic form of SVD. Vasculitis is an example of inflammatory and/or immunologically mediated SVD, and one rare cause of SVD is postradiation angioopathy.

The vessel changes in SVD include obliteration, occlusion, elongation and tortuosity. These changes lead to increased resistance, impaired autoregulation, and fluctuating or decreased flow along with ischemia (Román et al. 2002, Smith 2010, Brown and Thore 2011). Further vessel influence in SVD relates to endothelial dysfunction, including blood-brain barrier and carrier change (Wardlaw et al. 2009, Knottnerus et al. 2009, Hassan et al. 2003), extravasation of plasma proteins (Pantoni et al. 2002) and perivascular changes (Lammie and Wardlaw 1999). One feature of SVD is decreased vascular density and, for example, cholinergic deafferentation of the small vessels. Phenotypic modulation of smooth muscle cells in the small vessels, from contractile to synthetic phenotype, has also been suggested as a mechanism behind SVD (Fujita et al. 2008), leading to changes in the neuropil including microglial activation, loss of oligodendrocytes and demyelination.
Other factors related to SVD are oxidative stress, inflammatory factors and apoptosis (Brown and Thore 2011). In addition of importance are systemic vascular, cardiac and carotic hemodynamic changes, as well as decreased venous drainage related to, for instance, venous collagenosis (Black et al. 2009), obstructive sleep apnea (Robbins et al. 2005) and chronic obstructive pulmonary disease (COPD).

### 2.1.2 CLINICAL AND NEURORADIOLOGICAL PRESENTATION OF CEREBRAL SMALL-VESSEL DISEASE

Cerebral SVD presents clinically either as lacunar stroke with an acute and focal neurological deficit, or as more diffuse conditions such as gait instability (Baezner et al. 2008), urinary incontinence (van Straaten et al. 2006), progressive cognitive decline and dementia (Prins et al. 2004, Inzitari et al. 2009, Verdelho et al. 2010, Jokinen et al. 2009b) and mood disorders (Teodorczuk et al. 2010). The four main clinical lacunar stroke syndromes are pure motor stroke, pure sensory stroke, sensorimotor stroke, and ataxic hemiparesis, followed by some other less common syndromes (Fisher 1982, Donnan et al. 1993).

A subcortical location is the common factor for the neuroradiological features of cerebral SVD, which are either ischemic changes, bleeds or venous changes (Pantoni, 2010). Ischemic changes include WMC, lacunae, enlarged perivascular changes (état criblé, or cribriform state) and cortical microinfarcts. Bleeds include aneurysmatic bleeds, lobar hemorrhages and microscopic bleeds. Venous changes such as venous collagenosis involve, for example, deep galenic veins but these changes are less well characterized than arterial changes (Black et al. 2009).

The term leukoaraiosis (from the Greek leuko for ‘white’ and araiosis for ‘rarefaction’) was introduced more than 20 years ago to describe the hypodense visualization of WMC in CT (Hachinski et al. 1987). In MRI, WMC presents as periventricular and deep white matter areas that are bilaterally and symmetrically sited in the hemispheres and that appear hyperintense in T2-weighted and fluid-attenuated inversion recovery images (FLAIR). Periventricular changes appear in the form of caps, lining or halo and deep white matter changes appear as focal or confluent, according to the grade of severity (Mäntylä et al. 1997). With newer MRI techniques, such as diffusion tension imaging (DTI), susceptibility weighted imaging (SWI) and functional MRI, microangiopathic markers of SVD and white matter tract integrity might be detected and followed more accurately than before (Helenius et al. 2002, Schmidt et al. 2004, Peurala et al. 2008, Black et al. 2009, Pantoni 2010), but the documentation is still scarce.

SVD is a complex pathological process ranging from asymptomatic to symptomatic WMC through to bleeds and multiple lacunar infarcts, with symptoms ranging from gait disturbance to cognitive impairment. Citing Hachinski (2008), ignoring small strokes can cause big trouble.
2.1.3 RISK FACTORS OF CEREBRAL SMALL-VEssel DISEASE

In some studies among elderly patients (mean age of 63–68 years) increasing age and arterial hypertension have been the risk factors for WMC (Wiszniewska et al. 2000, Fu et al. 2004). In young patients aged up to 49 years type 1 diabetes has been demonstrated to be the strongest prognostic factor for WMC and silent infarcts (Putaala et al. 2009a). On the other hand, SVD was the most common stroke etiology among young stroke patients with type 1 or type 2 diabetes (Putaala et al. 2011a). Also in elderly patients (≥85 years) diabetes has been associated with development of vascular pathology, which alone or together with Alzheimer’s disease pathology has resulted in increased dementia risk (Ahtiluoto et al. 2010). The LADIS (Leukoaraiosis and Disability in the Elderly) Study among patients with mean age 74 years confirmed that age, arterial hypertension and lacunar strokes were the major determinants of WMC, whereas smoking and high cholesterol provided additional risk (Basile et al. 2006, Verdelho et al. 2010). In another study smoking was associated with progression of WMC and lacunar infarcts in a 3-year follow-up (van Dijk et al. 2008). A low serum concentration of vitamin B12 was associated with WMC volume in one study (Pieters et al. 2009), and a high homocysteine level was a risk factor particularly for WMC but also for isolated lacunar stroke in another study (Hassan et al. 2004).

On the other hand, according to two consecutive meta-analysis (Jackson and Sudlow 2005, Jackson et al. 2010) the risk factor profile for the SVD subtype of stroke—i.e. lacunar stroke—was largely similar as with other subtypes of stroke. According to these authors the assertion that hypertension and diabetes would be particularly associated with lacunar infarction may arise from bias caused by the use of a risk-factor based classification of stroke subtypes. Furthermore, lacunar stroke appeared less likely to be caused by embolism from the heart or proximal arteries (Jackson et al. 2010). However, the clinical data concerning cardiac and carotid embolic sources in patients with SVD is conflicting (Lammie and Wardlaw 1999), with some studies showing a low frequency of these sources but others suggesting that they may be important (Patankar et al. 2006, Altaf et al. 2006, van Dijk et al. 2008).

According to the current evidence hypertension and diabetes are risk factors for WMC and for stroke in general, not especially for lacunar stroke. The data concerning cardiac and carotid embolic sources is conflicting.

2.1.4 THERAPEUTIC CHALLENGES IN CEREBRAL SMALL-VEssel DISEASE

Cerebral SVD has been associated with elevated risk for hemorrhagic complications after intravenous thrombolysis of an acute ischemic stroke (Neumann-Haefelin et al. 2006, Palumbo et al. 2007) and reduced benefit from carotid endarterectomy (Streifler et al. 2002), including the risk of perioperative complications (Arshad et
However, the presence of SVD cannot be taken as a contraindication for thrombolysis and carotid endarterectomy (Pantoni 2010). A reduced dosage of anticoagulants has been recommended by some authors for patients with a clear manifestation of cerebral SVD (Gorter et al. 1999, Smith et al. 2002), bearing in mind microbleeds and blood-brain barrier dysfunction, while others suggest that since the risk-benefit ratio has not been well delineated, the degree of WMC should not influence clinical decision-making at present (Norrving 2008b).

The use of antiplatelet drugs such as aspirin, aspirin plus dipyridamole and ticlopidine has shown equal efficiency in secondary stroke prevention after stroke caused by SVD (Bousser et al. 1983, Gent et al. 1989, CAST 1997). In one clinical trial, cilostazol, an antithrombotic and vasodilating drug, reduced the risk of recurrent stroke especially in patients with lacunar infarction, suggesting that cilostazol could have a specific effect against SVD (Gotoh et al. 2000).

The PROGRESS (Perindopril Protection Against Recurrent Stroke Study) and the PROGRESS MRI substudy have emphasized the importance of anti-hypertensive treatment in prophylaxis against WMC (Dufouil et al. 2005, Schiffrin et al. 2005). In the PROGRESS study, however, the central mechanism was probably the influence of the ACE-inhibitor on the endothelium and not on blood pressure. Patients with SVD also seem to benefit from high-dose statin therapy (atorvastatin 80 mg) in addition to those with large-vessel stroke (Amarenco et al. 2009). In fact, all the drugs targeted on vascular risk factors seem of potential interest from the SVD perspective. In addition, vitamin B12 substitution and homocysteine lowering therapy are suggested to have preventive potential (Hassan et al. 2003, Pieters et al. 2009). To date, there is no anti-dementia drug with indication vascular cognitive decline/dementia, although some indirect evidence of the effect of anti-dementia drugs in vascular dementia can be found from trials (Pantoni 2010).

The ongoing Secondary Prevention of Small Subcortical Strokes (SPS3) trial is specially focused on cerebral SVD, with the prevention of recurrent stroke and reduction of cognitive decline as the primary outcomes (Benavente 2005, Pergola et al. 2007). The enrolment for this trial is still ongoing, the purpose being to compare two antiplatelet regimens (aspirin vs aspirin plus clopidogrel) with each other and, furthermore, to compare intensive blood pressure control with standard blood pressure control.

Neuroimaging evaluation of WMC has been suggested as a surrogate marker for assessing the efficacy of treatment in cerebral SVD (Schmidt et al. 2004). In the PROGRESS MRI substudy (Dufouil et al. 2005), administration of an ACE-inhibitor and a diuretic delayed the progression of WMC in patients with clinical stroke.

To date, the primary and secondary prevention of stroke have mainly applied to large-vessel pathology, but ongoing and future research may reveal specific therapies for SVD.
2 REVIEW OF THE LITERATURE

2.2 FACTORS AFFECTING POSTSTROKE SURVIVAL

Even though the poststroke mortality rate has decreased, stroke in general is associated with a greater than 50% risk of death during the subsequent 5 years and with a more than 70% risk of death within 10 years poststroke (Eriksson and Olsson 2001, Vernino et al. 2003). The factors that affect poststroke mortality vary, to a degree, according to the length of follow-up. Definitions of the short-term, mid-term and long-term also vary, but follow-up to from 30 days to 3 years is considered short-term, from 3 to 5 years mid-term and 5 years or more long-term, which is in line with previous publications (Norrving 2003, Carter et al. 2007, Pendlebury and Rothwell 2009). The prognosis up to 30 days or less can be considered more attributable to the acute event itself than to specific risk factors (Carter et al. 2007).

Advancing age is a predictor of short-term, mid-term and long-term survival for up to 12 years (Hu et al. 2005, Vernino et al. 2003, Kim et al. 2009). Stroke severity, as reflected by the baseline National Institute of Health (NIH) Stroke Scale score, predicts outcome, including mortality, for up to 3 months (Adams et al. 1999), but thereafter modified Rankin Scale (mRS; van Swieten et al. 1988) is preferred. A more severe stroke relates to an adverse outcome at several time points, ranging from one week to 5 years (Elneihoum et al. 1998, Frankel et al. 2000, Hankey 2003, Saposnik et al. 2008, Wahlgren et al. 2008, Kissela et al. 2009).

The influence of the subtype of ischemic stroke on mortality varies according to the length of the follow-up. In short-term studies cardioembolic stroke has usually been associated with the highest and SVD with the lowest mortality (Grau et al. 2001, Kolominsky-Rabas et al. 2001), whereas long-term studies have shown more variable results (Petty et al. 2000, Eriksson and Olsson 2001, Staaf et al. 2001). These studies are reviewed in detail below (2.2.4).

Cardiac diseases—i.e. cardiac failure, coronary heart disease and atrial fibrillation—are important predictors of short-term and long-term mortality after stroke (Dennis et al. 1993, Hankey et al. 1998, Vernino et al. 2003, Marini et al. 2005, Wahlgren et al. 2008). Of the vascular risk factors hypertension, diabetes, and smoking have been associated with mortality in stroke patients in both short-term and long-term follow-ups (Wolf et al. 1991, Dennis et al. 1993, Vernino et al. 2003, Hu et al. 2005, Rothwell et al. 2005, Van Wijk et al. 2005, Wahlgren et al. 2008). One study has showed that risk stratification score CHADS2 (Congestive heart failure, Hypertension, Age, Diabetes, Stroke or TIA) may be useful not only in assessing stroke risk but also in assessing all-cause mortality risk up to 5 years after stroke (Henriksson et al. 2010).

A previous stroke or transient ischemic attack (TIA) worsens prognosis at one month poststroke (Kaarisalo et al. 2005) and up to 7 years thereafter (Petty et al. 2000, Carter et al. 2007). However, in contrast to the early risk after a TIA and stroke, the long-term risks seem to be more dependent on the underlying vascular
risk factors than the characteristics of the event itself, according to a review by Pendlebury and Rothwell (2009). Poststroke dementia has been found to increase mortality in follow-ups extending to up to 5 years (Tatemichi et al. 1994) and 10 years (Desmond et al. 2002), and poststroke depression has been related with increased mortality in a 3-year follow-up (Williams et al. 2004) and a 10-year follow-up (Morris et al. 1993).

Vascular risk factors and cardiac diseases are important predictors of poststroke mortality irrespective of the length of follow-up, but influence of stroke subtype varies according to the selected time span.

2.2.1 POSTSTROKE DEMENTIA AND SURVIVAL

In community-based studies the prevalence of poststroke dementia among stroke survivors is approximately 30%, and in hospital based studies the prevalence ranges from 6% to 32% depending on the mean age of the study population, the delay between stroke and cognitive assessment, and the criteria for dementia used (Leys et al. 2005). Incidence studies indicate that the risk of poststroke dementia is highest within 6–12 months after stroke and remains double that of the normal population even after 12 months (Leys et al. 2005). Previous documentation from the Helsinki Stroke Aging Memory (SAM) study has showed that the frequency of clinically judged dementia, diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition (DSM-III; APA 1980), after first-ever stroke was 24.2% which was near the corresponding frequency in the whole cohort including also patients with previous stroke. Therefore, the occurrence of even a single stroke is important from the point of view of the development of cognitive decline (Pohjasvaara et al. 1997, Pohjasvaara et al. 1998).

Poststroke dementia is an important category of vascular cognitive impairment (Moorhouse and Rockwood 2008, Roman et al. 2004). In addition to the vascular burden, poststroke dementia also relates to the degenerative burden on the brain (Snowdon et al. 1997). The importance of vascular factors as the cause of Alzheimer disease is still under discussion (Roman and Royall 2004). At least stroke seems to be able to initiate a vascular exacerbation that increases the likelihood of a clinical dementia diagnosis in a patient with subclinical Alzheimer’s disease (Hachinski et al. 2006). Especially in the elderly, incident ischemic cerebrovascular disease relates to a clinical expression of dementia associated with Alzheimer’s disease pathology (Snowdon et al. 1997, Tyas et al. 2007). It has been suggested that SVD-induced leakage of apolipoprotein E might represent a pathogenetic link between SVD and Alzheimer’s disease (Utter et al. 2008).
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Number of patients</th>
<th>Follow-up</th>
<th>Diagnosis based on</th>
<th>Mean/median age</th>
<th>Poststroke dementia %</th>
<th>First-ever stroke %</th>
<th>Female sex %</th>
<th>Low education &lt;8 years %</th>
<th>Myocardial infarction or coronary artery disease %</th>
<th>Cardiac failure %</th>
<th>Hypertension %</th>
<th>Peripheral arterial disease %</th>
<th>Diabetes %</th>
<th>Current smoking %</th>
<th>Severe stroke %</th>
<th>RR or HR*</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tatemichi et al. 1994</td>
<td>USA</td>
<td>251</td>
<td>5 years</td>
<td>DSM-IIIR</td>
<td>72</td>
<td>26</td>
<td>-</td>
<td>55</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>-</td>
<td>-</td>
<td>RR 3.1</td>
<td>1.8-5.4</td>
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<tr>
<td>Desmond et al. 2002</td>
<td>USA</td>
<td>453</td>
<td>10 years</td>
<td>DSM-III</td>
<td>72</td>
<td>26</td>
<td>76</td>
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<td>73</td>
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<td>34</td>
<td>58</td>
<td>RR 4.5</td>
<td>1.6-3.4</td>
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<tr>
<td>Barba et al. 2002</td>
<td>Spain</td>
<td>324</td>
<td>29 months</td>
<td>DSM-IV</td>
<td>69</td>
<td>30</td>
<td>84</td>
<td>47</td>
<td>93%</td>
<td>12</td>
<td>6</td>
<td>13</td>
<td>60</td>
<td>-</td>
<td>26</td>
<td>47</td>
<td>RR 8.5</td>
<td>3.4-20.9</td>
</tr>
<tr>
<td>Hénon et al. 2003a</td>
<td>France</td>
<td>142</td>
<td>3 years</td>
<td>DSM-IV</td>
<td>75</td>
<td>31</td>
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<td>21</td>
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<td>11</td>
<td>12</td>
<td>17</td>
<td>RR 418</td>
<td>2.7-14.6</td>
</tr>
<tr>
<td>Appelros et al. 2005</td>
<td>Sweden</td>
<td>327</td>
<td>1 year</td>
<td>ICD-10</td>
<td>77</td>
<td>100</td>
<td>55</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>HR 1.8</td>
<td>1.1-2.9</td>
</tr>
<tr>
<td>Melkas et al. 2009</td>
<td>Finland</td>
<td>451</td>
<td>12 years</td>
<td>DSM-III</td>
<td>72</td>
<td>26</td>
<td>80</td>
<td>49</td>
<td>31%</td>
<td>19</td>
<td>22</td>
<td>19</td>
<td>48</td>
<td>12</td>
<td>25</td>
<td>50%</td>
<td>HR 1.53</td>
<td>1.15-2.04</td>
</tr>
</tbody>
</table>

DSM, Diagnostic and Statistical Manual of Mental Disorders. ICD, International Statistical Classification of Diseases. * Results regarding poststroke dementia as a predictor of survival, relative risk or hazard ratio. 1 Mean education 10 years. 2 Mean Stroke Severity Scale score 6.5. 3 Current or former smoking. 4 Stroke Severity Scale ≥4. 5 Prestroke dementia 10%. 6 Below high-school. 7 For any poststroke dementia. For prestroke dementia, RR 2.1, 95% CI 1.2-3.6, and for new-onset poststroke dementia, RR 6.3, 95% CI 2.3-17.3. 8 Prestroke dementia 11%. 9 Defined as Orgogozo scale score <50. 10 For new-onset poststroke dementia. For prestroke dementia, RR 5.0, 95% CI 1.8-14.0. 11 No data on poststroke dementia, but prestroke dementia 14%. 12 For prestroke dementia. 13 Education ≤6 years.
Prior studies that have investigated the influence of poststroke dementia on survival are summarized in Table 1. Tatemichi and colleagues (1994; N=251, follow-up 5 years) and Desmond and colleagues (2002; N=453, follow-up 10 years) showed that poststroke dementia is associated with poor poststroke survival after adjusting for major confounders. The study by Hénon and colleagues (2003a; N=142, follow-up 3 years), and the study by Barba and colleagues (2002; N=324, follow-up 29 months) including also patients with intracranial hemorrhages showed a similar poor poststroke survival for patients with poststroke dementia. Populations in all these studies have included both patients with a first-ever stroke and those with a previous stroke, but possible differences in survival between these two groups were not analyzed.

An additional negative influence of prestroke dementia on the poststroke survival was reported by Barba et al. (2002) and by Appelros et al. (2005) in a study where only prestroke dementia was investigated. However, Hénon et al. (2003a) found that the mortality rate did not differ between patients with prestroke and new-onset poststroke dementia.

**Summary:** Poststroke dementia is known to impair poststroke survival, but there is less documentation on the additional influence of prestroke cognitive decline and previous stroke.

### 2.2.2 POSTSTROKE COGNITIVE IMPAIRMENT AND SURVIVAL

Poststroke cognitive impairment consists of decline in various cognitive domains such as memory, language, visuospatial and constructional abilities (Tatemichi et al. 1994, Bowler et al. 1994) and also in executive function (Glosser and Goodglass 1990, Della Sala et al. 1993). Poststroke cognitive impairment is frequent – up to 65%–78% of patients demonstrate cognitive decline (Tatemichi et al. 1994, Pohjasvaara et al. 1998) and, as mentioned above, up to 32% of patients demonstrate poststroke dementia (Leys et al. 2005). In a population-based study (Patel et al. 2002), the proportion of cognitively impaired subjects (Mini Mental Status Examination MMSE<25; Folstein et al. 1975) was found to be 38% at 3 months poststroke, and in a hospital-based study 28% of the patients had an MMSE<24 at 1 month poststroke (House et al. 2001). Studies among aphasic patients have indicated that memory deficits in these patients appeared not simply as a consequence of language disorders but as a concurrent impairment of memory process (Beeson et al. 1993), and that memory deficits could not be explained by depression (Kauhanen et al. 2000).

Global measures of cognition—e.g. MMSE (Friedman 1991, Friedman 1994, House et al. 2001, Patel et al. 2002) and similar short mental status tests (Woo et al. 1992)—have been related to a poor survival in poststroke studies with up to 4-year follow-up. However, two short 1-year studies demonstrate that MMSE is not an independent predictor of poststroke survival (Thomassen et al. 1999, Altieri et
A single study utilizing short 10 item mental status questionnaire showed that cognitive impairment is an independent predictor of poststroke survival for up to 6 years (Wang et al. 2000).

Studies on the effect of specific cognitive domains on poststroke survival are limited. In an investigation among patients with first-ever stroke, severe aphasia was independently associated with poor survival (Moulin et al. 1997). Deficits in specific cognitive domains such as verbal, visuomotor, and memory performance, and reaction time have previously been associated with shortened survival at the general population level (Shipley et al. 2006, Portin et al. 2001). Cognitive impairment no dementia (CIND) has been related to impaired survival in studies of community-based populations where stroke has not been regarded (Ingles et al. 2003, Tuokko et al. 2003, Hsiung et al. 2006). In contrast, no association was found between neuropsychological variables and survival in another study with 3-year follow-up, where selected items from standardized tests were used (Johnston et al. 2004).

**Summary:** The influence of cognitive deficits on poststroke survival has not been studied previously using comprehensive neuropsychological evaluation.

### 2.2.3 POSTSTROKE DEPRESSION AND SURVIVAL

The mean prevalence of poststroke major depression in community studies has been 14%, and that of poststroke minor depression 9%. In hospital studies the mean prevalence of poststroke major depression has been 19% and that of poststroke minor depression 30% (Robinson 2006). Stroke survivors are predisposed to depressive symptoms independently of functional disability or previous depressive symptoms later, even years after the stroke (Whyte et al. 2004). In a previous report from the Helsinki Stroke Aging Memory (SAM) study, the frequency of any depression at 3 months poststroke was 40% (Vataja et al. 2001).

Poststroke depression has been suggested as a subtype of vascular depression, a late-onset form of depression in patients with established cerebrovascular disease (CVD) and/or risk factors of CVD (Alexopoulos et al. 1997, Krishnan et al. 1997). A typical feature of vascular depression is significant impairment in executive functions, including planning, initiation, sequencing and monitoring of complex goal-directed behavior (Lockwood et al. 2002), as well as impairment in activities of daily living (ADL) (Pohjasvaara et al. 2002).

Alexopoulos et al. (2002) have stated that executive dysfunction, but not other cognitive abnormalities, influences the course of geriatric depression. This suggests that executive dysfunction is an integral part of some syndromes of geriatric depression rather than a coincidental dysfunction. According to Alexopoulos et al. (2002), depression-executive dysfunction syndrome (DES) has a distinctive clinical presentation with reduced fluency, impaired visual naming, psychomotor retardation, loss of interest in activities, and paranoia.
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Number of patients</th>
<th>Follow-up</th>
<th>Diagnosis based on</th>
<th>Mean/median age</th>
<th>Poststroke depression %</th>
<th>First-ever stroke %</th>
<th>Female sex %</th>
<th>Living alone %</th>
<th>Myocardial infarction or coronary artery disease %</th>
<th>Cardiac failure %</th>
<th>Atrial fibrillation %</th>
<th>Hypertension %</th>
<th>Peripheral arterial disease %</th>
<th>Diabetes %</th>
<th>Current or former smoking %</th>
<th>Severe stroke %</th>
<th>OR/HR*</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morris et al. 1993</td>
<td>Australia</td>
<td>91</td>
<td>10 years</td>
<td>DSM-III</td>
<td>62</td>
<td>41</td>
<td>82</td>
<td>41</td>
<td>-</td>
<td>24</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>12</td>
<td>-</td>
<td>OR 3.7</td>
<td>1.1-12.2</td>
</tr>
<tr>
<td>Åström et al. 1993</td>
<td>Sweden</td>
<td>80</td>
<td>3 years</td>
<td>DSM-III</td>
<td>73</td>
<td>31</td>
<td>80</td>
<td>39</td>
<td>38</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>House et al. 2001</td>
<td>UK</td>
<td>448</td>
<td>2 years</td>
<td>ICD-10</td>
<td>71</td>
<td>22</td>
<td>79</td>
<td>46</td>
<td>40</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>35</td>
<td>OR 2.2</td>
<td>1.2-4.0</td>
<td></td>
</tr>
<tr>
<td>Johnston et al. 2004</td>
<td>UK</td>
<td>101</td>
<td>3 years</td>
<td>HADS</td>
<td>71</td>
<td>-</td>
<td>71</td>
<td>49</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Williams et al. 2004</td>
<td>USA</td>
<td>51,119</td>
<td>3 years</td>
<td>ICD-9</td>
<td>65</td>
<td>5</td>
<td>-</td>
<td>2</td>
<td>2</td>
<td>-</td>
<td>9</td>
<td>10</td>
<td>61</td>
<td>-</td>
<td>30</td>
<td>30</td>
<td>HR 1.13</td>
<td>1.07-1.22</td>
<td></td>
</tr>
<tr>
<td>Melkas et al. 2010</td>
<td>Finland</td>
<td>257</td>
<td>12 years</td>
<td>DSM-III-R</td>
<td>71</td>
<td>39</td>
<td>80</td>
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<td>18</td>
<td>18</td>
<td>46</td>
<td>11</td>
<td>24</td>
<td>52</td>
<td>33</td>
</tr>
</tbody>
</table>

HADS, Hospital Anxiety and Depression scale. NA, no association found. DSM, Diagnostic and Statistical Manual of Mental Disorders. ICD, International Statistical Classification of Diseases. * Results regarding poststroke depression as a predictor of survival, odds ratio or hazard ratio. ^ For any poststroke depression, for patients with depression-executive dysfunction syndrome (DES) vs. patients with neither depression nor executive dysfunction, HR 1.63, 95% confidence interval 1.05-2.52.
It has been suggested that in patients with DES, brain infarcts and WMC affecting frontostriatal circuits are associated with both depression and executive dysfunction (Vataja et al. 2005, Teodorczuk et al. 2007). However, personal vulnerability and psychosocial stress caused by severe disease also relate to poststroke depression (Whyte and Mulsant 2002). The relationship between depression and CVD is bidirectional, and several mechanisms have been suggested to link these conditions with each other (Thomas et al. 2004, Teper and O’Brien 2008, Robinson et al. 2008).

The association between depression in general and mortality in cardiovascular and cerebrovascular diseases has been indicated by several studies (Everson et al. 1998, Ramasubbu and Patten 2003). Looking at poststroke patients and their overall survival, the influence of depression seems to be more controversial. Previously, four studies have investigated the influence of poststroke depression on survival with at least 3-year follow-up. In two of these studies, depression was associated with impaired poststroke survival (Morris et al. 1993, Williams et al. 2004), while the other two studies found no association (Åström et al. 1993, Johnston et al. 2004; Table 2). Furthermore, one study with a follow-up of 2 years has indicated that self-reported mood disorder is an independent predictor of survival (House et al. 2001). The prevalence of concurrent executive dysfunction has not been investigated in these studies, which may be a source of variability.

Poststroke depression and dementia seem to be closely linked conditions, and vascular depression and more specifically poststroke depression can be considered a warning sign for emerging vascular cognitive impairment (Steffens et al. 2003).

**Summary:** Current evidence on the potential association between poststroke depression and survival is controversial, and the influence of concurrent executive dysfunction has not been taken in account in previous studies.

### 2.2.4 The Effect of Stroke Subtype on Poststroke Survival

As reviewed by Norrving (2003), the documentation on survival in different stroke subtypes arises mostly from short-term follow-up studies with up to 5 years of observation. Most earlier data suggest that short-term prognosis is generally favorable after an ischemic stroke due to small-vessel disease (SVD), i.e., the traditional lacunar stroke. For example, in a study by Grau and colleagues (2001), the mortality rate at 3 months after ischemic stroke in patients admitted to hospital was 23% for cardioembolic (CE) stroke, 16% for large-artery atherosclerotic (LAA) stroke, and 3% for the SVD subtype of stroke. In two other population-based studies, the mortality rates at one year poststroke were 42% for CE, 28% for LAA and 19% for SVD (Anderson et al. 1994) and at two years, 45% for CE, 42% for LAA and 15% for SVD (Kolominsky-Rabas et al. 2001). Moreover, in a mortality analysis of young ischemic stroke patients aged up to 49 years, patients with SVD subtype of stroke similarly fared best during the 5-year follow-up (Putaala et al. 2009b).
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Number of patients</th>
<th>Follow-up</th>
<th>Subtype classification used</th>
<th>Mean/median age</th>
<th>SVD subtype of stroke %</th>
<th>First-ever stroke %</th>
<th>Female sex %</th>
<th>Low education ≤ 6 years %</th>
<th>Myocardial infarction or coronary artery disease %</th>
<th>Cardiac failure %</th>
<th>Atrial fibrillation %</th>
<th>Hypertension %</th>
<th>Peripheral arterial disease %</th>
<th>Diabetes %</th>
<th>Current smoking %</th>
<th>Severe stroke %</th>
<th>Mortality rate LAA</th>
<th>Mortality rate CE</th>
<th>Mortality rate SVD</th>
<th>Mortality rate undetermined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson et al. 1994</td>
<td>Australia</td>
<td>492</td>
<td>1 yr</td>
<td>Own criteria</td>
<td>73</td>
<td>6</td>
<td>72</td>
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<td>19</td>
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<td>25</td>
<td>27</td>
<td>42</td>
<td>19</td>
<td>80</td>
</tr>
<tr>
<td>Petty et al. 2000</td>
<td>USA</td>
<td>442</td>
<td>5 yrs</td>
<td>NINDS</td>
<td>74</td>
<td>16</td>
<td>100</td>
<td>58</td>
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<td>32</td>
<td>80</td>
<td>35</td>
<td>47</td>
</tr>
<tr>
<td>Kolominsky-Rabas et al. 2001</td>
<td>Germany</td>
<td>583</td>
<td>2 yrs</td>
<td>TOAST</td>
<td>73</td>
<td>23</td>
<td>100</td>
<td>57</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>-</td>
<td>42</td>
<td>45</td>
<td>15</td>
<td>39</td>
</tr>
<tr>
<td>Eriksson et al. 2001</td>
<td>Sweden</td>
<td>339</td>
<td>14 yrs</td>
<td>Own criteria</td>
<td>74</td>
<td>14</td>
<td>77</td>
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<td>-</td>
<td>20</td>
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<td>38</td>
<td>84</td>
<td>96</td>
<td>75</td>
<td>-</td>
</tr>
<tr>
<td>Carter et al. 2007</td>
<td>UK</td>
<td>545</td>
<td>7 yrs</td>
<td>OCSP</td>
<td>72</td>
<td>34</td>
<td>70</td>
<td>50</td>
<td>-</td>
<td>28</td>
<td>-</td>
<td>19</td>
<td>41</td>
<td>13</td>
<td>15</td>
<td>57</td>
<td>-</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Melkas et al. 2011</td>
<td>Finland</td>
<td>486</td>
<td>12 yrs</td>
<td>TOAST</td>
<td>71</td>
<td>13</td>
<td>80</td>
<td>49</td>
<td>31</td>
<td>19</td>
<td>22</td>
<td>20</td>
<td>47</td>
<td>12</td>
<td>25</td>
<td>50</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

NINDS, National Institute of Neurological Diseases and Stroke Data Bank criteria. TOAST, Trial of Org 10172 in Acute Stroke Treatment criteria. OCSP, Oxfordshire Community Stroke Project criteria. NA, no association found. ¹Current or former smoking. ²According to Motricity Index, severe paresis. ³Modified Rankin scale 4-5. ⁴SVD vs. non-SVD, HR 1.60, 95% confidence interval 1.06-2.41.
A population based study with a 5-year follow-up and adjustment for age, sex, cardiac comorbidities, and stroke severity found that the survival curve after lacunar stroke lay in between CE and LAA, the former with the poorest and the latter with the best survival (Petty et al. 2000). The prestroke functional status was the worst among those patients who subsequently developed cardioembolic disease, which probably reflects a higher prevalence of heart disease and cardiac-related prestroke disability among those with cardioembolic stroke, although the frequencies are not detailed.

Among patients admitted to hospital in another study, the probability of death within 14 years of follow-up was highest for CE index stroke, followed by large-vessel stroke, whereas patients with lacunar stroke had the best outcome, although the differences were small (Eriksson and Olsson 2001). Multivariate statistical analysis was not performed in this study and the diagnosis of lacunar stroke was based on clinical syndromes only. It is therefore possible that the burden of lacunes and also their influence on survival was underestimated.

Evidence of less favorable prognosis for SVD after longer follow-up comes from a study with 10 years of follow-up, where the survival of patients with pure motor stroke from a presumed lacunar infarct were compared to the survival of the general population (Staaf et al. 2001). The risk of death after pure motor stroke was similar to that in the general population during the first 5 years, but beyond that time point the risk increased by 10%−15% when compared with the general population. In another study, the long-term risk of death after lacunar stroke increased from 27.4% at 5 years to 60% at 10 years, and finally, to 75% at 14 years (Arboix and Marti-Vilalta 2009).

**Summary:** The SVD subtype of stroke has been generally associated with better short-term outcome than other subtypes, but long-term outcome is not well documented.

### 2.2.5 POSTSTROKE DELIRIUM AND SURVIVAL

Five studies have been previously published on delirium in the acute stroke setting with a focus on associated factors and outcome (Gustafson et al. 1991, Hénon et al. 1999, Caeiro et al. 2004, Sheng et al. 2006, McManus et al. 2009; Table 4). These studies have shown the frequency of poststroke delirium to vary between 13−48%, depending on the timing, frequency and type of the assessments. These studies also show an increased risk for nursing home replacement among patients with poststroke delirium. Four out of five studies have shown poststroke delirium to be associated with increased mortality from discharge to up to 12 months, but to our knowledge no studies to date have investigated the influence of poststroke delirium on long-term mortality.
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Number of patients</th>
<th>Follow-up</th>
<th>Diagnosis based on</th>
<th>Timepoint for assessment</th>
<th>Poststroke delirium %</th>
<th>First-ever stroke %</th>
<th>Female sex %</th>
<th>Low education ≤8 years %</th>
<th>Myocardial infarction or coronary artery disease %</th>
<th>Atrial fibrillation %</th>
<th>Hypertension %</th>
<th>Periph. arterial disease %</th>
<th>Diab. %</th>
<th>Current smoking %</th>
<th>Severe stroke %</th>
<th>Prestroke cognitive decline %</th>
<th>Association with mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gustafson et al. 1991</td>
<td>Sweden</td>
<td>145</td>
<td>Discharge</td>
<td>DSM-III R</td>
<td>Week 1</td>
<td>73</td>
<td>48</td>
<td>-</td>
<td>-</td>
<td>541</td>
<td>43</td>
<td>17</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>yes</td>
</tr>
<tr>
<td>Hénon et al. 1999</td>
<td>France</td>
<td>202</td>
<td>6 months</td>
<td>DSM-IV ≤12 days</td>
<td>≤12 days</td>
<td>75</td>
<td>24</td>
<td>73</td>
<td>52</td>
<td>81</td>
<td>30</td>
<td>29</td>
<td>55</td>
<td>10</td>
<td>12</td>
<td>18</td>
<td>-</td>
<td>no</td>
</tr>
<tr>
<td>Caeiro et al. 2004</td>
<td>Portugal</td>
<td>218</td>
<td>Discharge</td>
<td>DRS Day 1</td>
<td>≤3 days</td>
<td>57</td>
<td>13</td>
<td>60</td>
<td>40</td>
<td>754</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>18</td>
<td>-</td>
<td>3</td>
<td>yes</td>
</tr>
<tr>
<td>Sheng et al. 2006</td>
<td>Australia</td>
<td>156</td>
<td>12 months</td>
<td>DSM-IV ≤3 days</td>
<td>≤3 days</td>
<td>79</td>
<td>25</td>
<td>72</td>
<td>47</td>
<td>-</td>
<td>30</td>
<td>31</td>
<td>72</td>
<td>21</td>
<td>53</td>
<td>-</td>
<td>-</td>
<td>yes</td>
</tr>
<tr>
<td>McManus et al. 2009</td>
<td>UK</td>
<td>82</td>
<td>1 month</td>
<td>DSM-III R ≤4 days</td>
<td>≤4 days</td>
<td>66</td>
<td>28</td>
<td>38</td>
<td>-</td>
<td>26</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>42</td>
<td>26</td>
<td>3</td>
<td>yes</td>
</tr>
<tr>
<td>Melkas et al. 2011</td>
<td>Finland</td>
<td>263</td>
<td>10 years</td>
<td>DSM-IV ≤7 days</td>
<td>≤7 days</td>
<td>71</td>
<td>19</td>
<td>81</td>
<td>49</td>
<td>28*</td>
<td>18</td>
<td>19</td>
<td>46</td>
<td>11</td>
<td>24</td>
<td>52*</td>
<td>33</td>
<td>9 no</td>
</tr>
</tbody>
</table>

DSM, Diagnostic and Statistical Manual of Mental Disorders. DRS, Delirium Rating Scale. 1 All cardiovascular disease, including myocardial infarction, cardiac failure, angina pectoris and atrial fibrillation. 2 Median Orgogozo score at admission 68.9. 3 According to IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly. 4 Less than 10 years of education. 5 Current or former smoking. 6 Barthel score <10 at admission. 7 Education ≤6 years.
Delirium and dementia have a close, bidirectional relationship. Dementia is a risk factor for delirium, whereas delirium may be an early sign of emerging dementia (Young and Inouye 2007, Rockwood et al. 1999, Rahkonen et al. 2000). Pre-existing dementia or cognitive decline has been associated with poststroke delirium (Gustafson et al. 1991, Hénon et al. 1999, Sheng et al. 2006), but these studies did not investigate the frequency of poststroke dementia.

Prestroke cognitive decline (Gustafson et al. 1991, Hénon et al. 1999) and stroke severity (Gustafson et al. 1991, Hénon et al. 1999, Sheng et al. 2006, McManus et al. 2009) have previously been related as risk factors to poststroke delirium. Low education has been identified as a risk factor in a more heterogeneous study population (Jones et al. 2006), but not in poststroke studies (Hénon et al. 1999, Caeiro et al. 2004). To the best of our knowledge, the frequency of dementia has not been investigated. However, Hénon et al. (1999) found that MMSE at 6 months was significantly lower in patients with poststroke delirium than in patients who did not suffer from it. An episode of poststroke delirium is considered an indicator of poor brain reserve capacity (Jones et al. 2010).

**Summary:** There is evidence supporting an association between poststroke delirium and increased mortality for up to 12 months, but its influence on long-term mortality has not been investigated.

### 2.3 CAUSES OF POSTSTROKE DEATH

According to earlier studies, death during the first week after stroke is attributable primarily to the direct effects of the stroke, such as brain edema with transtentorial herniation, whereas death during the first month after stroke seems attributable to potentially preventable causes, such as pulmonary embolism and respiratory infections (Viitanen et al. 1987, Bounds et al. 1981, Silver et al. 1984). In one study the proportion of vascular deaths decreased with time: of all deaths 75% were vascular at 1 month and 43% thereafter (Hartmann et al. 2001). The same study found that incident or recurrent stroke caused 57% of early poststroke deaths and 14% of long-term deaths.

Vernino et al. (2003) found in a population-based study that during the first month after cerebral infarction, mortality resulted predominantly from neurological complications, and later mortality remained high because of respiratory and cardiovascular causes. However, many epidemiological studies of long-term poststroke survival have not specifically evaluated the causes of death (Brown et al. 1996, Petty et al. 1998, Broderick et al. 1992).
2.4 FACTORS AFFECTING ISCHEMIC STROKE RECURRENCE

The cumulative risk of first stroke recurrence is substantial, and recurrent stroke is more disabling and fatal than first-ever stroke (Bonita et al. 1992). Long-term studies up to 10 years poststroke show recurrence rates ranging from 12 to 42% (Petty et al. 2000, Dhamoon et al. 2006, Mohan et al. 2009).

In general, the predictors of stroke recurrence are largely the same as the predictors of poststroke mortality. For example, Hankey and colleagues (2003) found that diabetes, previous TIA, atrial fibrillation, hypertension, high alcohol consumption, and increasing age predict long-term stroke recurrence. Mohan and colleagues (2009) also found that risk factors prior to an initial stroke had a significant role in predicting stroke recurrence for up to 10 years. On the other hand, stroke subtype and stroke severity do not seem to influence the recurrence (Mohan et al. 2009, Kolominsky-Rabas et al. 2001).

2.4.1 WHITE MATTER CHANGES AND STROKE RECURRENCE

White matter changes (WMC) are a frequent finding in brain imaging, especially in stroke patients (Leys et al. 1999, Helenius et al. 2002, Pohjasvaara et al. 2003, Wen and Sachdev 2004). Extensive WMC is a surrogate of small-vessel disease (SVD) (Erkinjuntti et al. 2000, Román et al. 2002, Oksala et al. 2009, Pantoni 2010). Severe WMC has been related to increased mortality both in elderly and young stroke patients (Oksala et al. 2009, Pataala et al. 2011b) and in those without stroke (Debette and Markus 2010, Kerber et al. 2006). Severe WMC has also been associated to adverse outcomes such as dependency, cognitive impairment and dementia (Prins et al. 2004, Inzitari et al. 2009, Verdelho et al. 2010, Jokinen et al. 2009b), depression (Teodorczuk et al. 2010), gait impairment and instability (Baezner et al. 2008), as well as a shift in modified Rankin Scale (mRS) toward less favorable outcome measured at 6 months poststroke (Arsava et al. 2009).

Two previous studies with a shorter follow-up period published after the year 2000 have shown a strong association between severe WMC and stroke recurrence (Fu et al. 2005, Hénon et al. 2003b; Table 5). Fu et al. (2005) followed 228 first-ever stroke patients, with a mean age of 68 years for an average of 23 months. All patients underwent brain MRI. The stroke recurrence rate was 43.7% for patients with severe WMC compared to 9.3% in patients with mild WMC, and there was an association between stroke recurrence and severe WMC (HR 4.18) after controlling for the classic risk factors. Hénon et al. (2003b) followed 202 stroke patients, with a median age of 75 years, 84% of whom had suffered their first-ever stroke. The WMC score as evaluated with CT scan was a strong predictor of stroke recurrence during the 3-year follow-up (RR 1.70).
Furthermore, in the setting of the North American Symptomatic Carotid Endarterectomy Trial—i.e. in patients with a transient ischemic attack or non-disabling stroke associated with internal carotid artery disease—the presence of WMC as detected by CT was associated with an increased risk of any stroke and of disabling or fatal stroke (Streifler et al. 2002). Here, the patients with widespread WMC also had the worst prognosis. In the setting of the LADIS study, the presence of vascular risk factors at baseline predicted both WMC progression and new lacunes over a 3-year period, and WMC progression and new lacunes were observed especially in patients with considerable WMC and lacunes at baseline (Gouw et al. 2008). Even earlier studies from the 1990s have showed an association between WMC and recurrent stroke in patients with TIA or minor stroke (van Swieten et al. 1992) and in patients with lacunar stroke (Miyao et al. 1992). WMC also relates with high degree of carotid stenosis (Patankar et al. 2006) and unstable plaques (Altaf et al. 2006).

**Summary:** WMC has been found to associate with stroke recurrence, but the evidence is limited to short-term follow-ups.
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Number of patients</th>
<th>Follow-up</th>
<th>Mean/median age</th>
<th>None to mild / moderate / severe WMC %</th>
<th>First-ever stroke %</th>
<th>Female sex %</th>
<th>Low education ≥ 50 years %</th>
<th>Myocardial infarction or coronary artery disease %</th>
<th>Cardiac failure %</th>
<th>Atrial fibrillation %</th>
<th>Hypertension %</th>
<th>Peripheral arterial disease %</th>
<th>Diabetes %</th>
<th>Current smoking %</th>
<th>RR/HR*</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fu et al. 2005</td>
<td>China</td>
<td>228</td>
<td>23 months</td>
<td>68</td>
<td>44/26/30</td>
<td>43</td>
<td>-</td>
<td>15</td>
<td>-</td>
<td>9</td>
<td>64</td>
<td>-</td>
<td>22</td>
<td>27</td>
<td>HR 4.2</td>
<td>2.0-8.6</td>
<td></td>
</tr>
<tr>
<td>Hénon et al. 2003b</td>
<td>France</td>
<td>202</td>
<td>3 years</td>
<td>75</td>
<td>66/24/10</td>
<td>84</td>
<td>52</td>
<td>-</td>
<td>30</td>
<td>-</td>
<td>54</td>
<td>-</td>
<td>12</td>
<td>18</td>
<td>RR 1.7</td>
<td>1.2-2.4</td>
<td></td>
</tr>
<tr>
<td>Melkas et al. (subm.)</td>
<td>Finland</td>
<td>320</td>
<td>5 (12) years</td>
<td>71</td>
<td>31/18/51</td>
<td>100</td>
<td>50</td>
<td>31</td>
<td>19</td>
<td>21</td>
<td>21</td>
<td>47</td>
<td>13</td>
<td>24</td>
<td>HR 1.8</td>
<td>1.1-3.0</td>
<td></td>
</tr>
</tbody>
</table>

* Results regarding severe WMC as a predictor of stroke recurrence, relative risk or hazard ratio. ¹Evaluation based on CT scan only. ²Current or former smoking.
3 AIMS OF THE PRESENT STUDY

The aim of the present study was to investigate poststroke mortality and morbidity from the small-vessel disease perspective in long-term follow-up:

1. To test the hypothesis that poststroke dementia impairs survival and that pre-stroke cognitive decline and previous stroke increase this influence (Study I).
2. To test the hypothesis that different cognitive deficits as well as cognitive impairment no dementia (CIND) associate with impair survival after stroke (Study II).
3. To test the hypothesis that poststroke depression impairs survival and that this effect is augmented in patients with concurrent executive dysfunction, i.e. depression-executive dysfunction syndrome (DES) (Study III).
4. To test the hypothesis that patients with acute stroke due to SVD—i.e. lacunar stroke syndrome—have an increased risk of long-term mortality when compared with those with a non-SVD subtype of stroke (Study IV).
5. To test the hypothesis that poststroke delirium associates with both increased long-term mortality and poststroke dementia (Study V).
6. To test the hypothesis that severe white matter changes (WMC), a surrogate of SVD, are associated with ischemic stroke recurrence (Study VI).
Table 6. Patient flow in the Helsinki Stroke Aging Memory study.

<table>
<thead>
<tr>
<th>Reason for non-enrolment</th>
<th>N=1622 Consecutive patients with suspected stroke</th>
<th>N=1149 Patients with ischemic stroke</th>
<th>N=642 Fulfilling inclusion criteria, invited to 3-month follow-up</th>
<th>N=486 Clinical evaluation at 3 months poststroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not fulfilling the current criteria for stroke</td>
<td>n=175</td>
<td>Age under 55 or over 85 years n=346</td>
<td>Death before the 3-month follow-up n=71</td>
<td>Reasons for non-enrolment in the sub-studies (number of study)</td>
</tr>
<tr>
<td>Intracerebral hemorrhage n=229</td>
<td>Subarachnoid hemorrhage n= 69</td>
<td>Not living in the city of Helsinki n=158</td>
<td>Refused n=82</td>
<td>Severe aphasia n=32 (I, II, III, V)</td>
</tr>
<tr>
<td>Patients with ischemic stroke n=1149</td>
<td></td>
<td>Not speaking Finnish n=3</td>
<td>Lost n=3</td>
<td>Severe hearing impairment n=1 (I, II, III, V)</td>
</tr>
<tr>
<td>Fulfilling inclusion criteria, invited to 3-month follow-up n=642</td>
<td></td>
<td></td>
<td></td>
<td>MRI not done n=63 (II, III, V, VI)</td>
</tr>
<tr>
<td>Death before the 3-month follow-up n=71</td>
<td></td>
<td></td>
<td></td>
<td>Severe illness n=12</td>
</tr>
<tr>
<td>Refused n=82</td>
<td></td>
<td></td>
<td></td>
<td>Obesity n=1</td>
</tr>
<tr>
<td>Lost n=3</td>
<td></td>
<td></td>
<td></td>
<td>Refusal n=21</td>
</tr>
<tr>
<td>Clinical evaluation at 3 months poststroke n=486</td>
<td>Reasons for non-enrolment</td>
<td></td>
<td></td>
<td>Claustrophobia n=2</td>
</tr>
<tr>
<td>(number of study)</td>
<td>in the sub-studies</td>
<td></td>
<td></td>
<td>Contraindication n=27</td>
</tr>
<tr>
<td>Severe aphasia n=32 (I, II, III, V)</td>
<td>(I, II, III, V)</td>
<td></td>
<td></td>
<td>Psychiatric examination not possible n=85 (III, V)</td>
</tr>
<tr>
<td>Severe hearing impairment n=1 (I, II, III, V)</td>
<td>MRI not done n=63 (II, III, V, VI)</td>
<td></td>
<td></td>
<td>Refused psychiatric examination n=30 (III, V)</td>
</tr>
<tr>
<td>MRI not done n=63 (II, III, V, VI)</td>
<td>Severe illness n=12</td>
<td></td>
<td></td>
<td>Neuropsychologic examination not possible  n=18 (II, III)</td>
</tr>
<tr>
<td>Severe illness n=12</td>
<td>Obesity n=1</td>
<td></td>
<td></td>
<td>Previous stroke n=98 (VI)</td>
</tr>
</tbody>
</table>
4 SUBJECTS AND METHODS

All six studies were conducted as a part of the Helsinki Stroke Aging Memory (SAM) study.

4.1 SUBJECTS AND STUDY PROTOCOL

The Helsinki SAM study is a prospective cross-sectional study examining the cognitive, functional and emotional consequences of ischemic stroke. The cohort comprised a consecutive series of all Finnish (Caucasian) patients with suspected stroke admitted to Helsinki University Central Hospital (n=1622) between 1 December 1993 and 30 March 1995, as described in detail previously (Pohjasvaara et al. 1997, Oksala et al. 2007). Patients aged 55 to 85 years living in Helsinki were included. Patients without ischemic stroke (n=175), presenting with intracerebral (n=229) or subarachnoid hemorrhage (n=69) were excluded. A total of 642 patients fulfilled the inclusion criteria and were invited to a follow-up visit 3 months later. Of these, 71 died (11.1%) before the 3-month follow-up, 82 refused (12.8%) and three were lost (0.5%) due to undefined causes. Finally, 486 (85.1% of the living patients) were included in the final SAM cohort (Mäntylä et al. 1999a).

Of these 486 patients, 396 underwent a brain MRI examination (Vataja et al. 2001). The reasons for not performing the MRI for 90 patients are detailed in Table 6. The study population included no patients with a recurrent stroke between the index stroke and the 3-month evaluation.

The study was approved by the Ethics committee of the Department of Clinical Neurosciences, Helsinki University Central Hospital, Finland. The study was explained to the patients, and informed consent was obtained.

A detailed medical and neurological history was taken as described previously (Pohjasvaara et al. 1997). The patients’ level of education was divided in two categories: low (0-6 years of formal education) and high (>6 years of formal education). Smoking habits were scored on admission as non-smokers and smokers (current or former). The history of cardiac risk factors (myocardial infarction, cardiac failure, atrial fibrillation), arterial hypertension, peripheral arterial disease, and diabetes was investigated by reviewing all available hospital records, in addition to a structured interview of the subject and a knowledgeable informant. A history of hypertension was defined at the time of study inclusion as systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥95 mmHg. Diabetes was defined as previously documented diagnosis, current use of insulin or oral antidiabetic medication, or fasting blood glucose >7.0 mmol/L. Stroke severity was assessed
using modified Rankin Scale (range 1-5; scores 3-5 indicate severe stroke) (van Swieten et al. 1988).

### 4.2 DIAGNOSIS OF DEMENTIA AND PRESTROKE COGNITIVE DECLINE (I, V)

Dementia was diagnosed using the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition (DSM-III) (APA 1980). The clinical mental status examination by the neurologist assessed the following domains: attention; orientation; memory recall; executive functions including abstract thinking, judgment, and problem solving; aphasia; apraxia; agnosia; motor control; constructional and visuospatial abilities; and personality change as detailed previously (Pohjasvaara et al. 1997). The clinical cognitive assessment also included the Folstein Mini Mental Status Examination (MMSE; maximum=30) (Folstein et al. 1975). In addition, social functioning was assessed using the Index of ADL (activities of daily living; Katz et al. 1970), the IADL scale (instrumental activities of daily living; Lawton et al. 1969), the Functional Activity Questionnaire (Pfeffer et al. 1982), the Blessed Functional Activity Scale (Blessed et al. 1968, Erkinjuntti et al. 1988), and the Barthel Index (Mahoney et al. 1965).

The assessment of prestroke cognitive decline was based on interviews with the patient and a knowledgeable informant (Pohjasvaara et al. 1999). The interviews included structured questions on abnormality in the cognitive domains as well as assessment of social functions before the index stroke. The beginning of the symptoms and their duration were enquired about, with particular focus on the period of one year preceding the index stroke. Based on all available history from the patient and the knowledgeable informant, a board-certified neurologist independently judged whether the patient had suffered prestroke cognitive decline or not. The category of patients with prestroke cognitive decline also included those with borderline and definite dementia.

### 4.3 NEUROPSYCHOLOGICAL EVALUATION (II)

A comprehensive neuropsychological evaluation was performed 3 months after the index stroke as detailed previously (Pohjasvaara et al. 1998). In brief, global cognitive function was measured with the MMSE. A score of ≤25 indicated cognitive impairment. Executive functions including attention, memory, language and overall evaluation of speech, as well as visuospatial and constructional abilities were assessed with standardized tests that are summarized in Table 7. Abnormality (impaired vs. not impaired) in each domain was judged with the use of normative data from a
random healthy Finnish population (2 SD or, if more than one test was used, 1 SD below the level of the norm in several tests indicated abnormality) (Ylikoski et al. 1993). The normal values were evaluated in different age groups.

Cognitive impairment without dementia—i.e. cognitive impairment no dementia (CIND; Tuokko et al. 2003)—was defined as cognitive impairment in any of the above-mentioned domains after the exclusion of patients with dementia. Of the patients with MMSE<25 (n=138), 94/138 (68.1%) had dementia at the 3-month follow-up. Furthermore, of these, 62/94 (66.0%) of these had suffered prestroke cognitive decline. The assessment of prestroke cognitive decline involved interviews with the patient and a knowledgeable informant, using structured questions. Dementia was defined according to DSM-III criteria (APA 1980). From the basic cohort of 486 patients, we first excluded those who had not been tested for dementia (n=35, 7.2%) and those who had dementia (n=115, 23.7%). We further investigated whether patients had impairment in any of the assessed domains. Fifty-two patients were excluded at this point because of missing values in the assessed domains at the same time as none of the existing values indicated impairment. Finally, there were 212 patients with CIND and 72 patients with no cognitive impairment.

### 4.4 PSYCHIATRIC EVALUATION (III, V)

The clinical psychiatric evaluation was carried out 12–20 weeks after the index stroke (Vataja et al. 2001). The examination included the computer-assisted structured interview Schedules for Clinical Assessment in Neuropsychiatry (Wing et al. 1990).
The severity of depression was measured using the Montgomery-Åsberg Depression Rating Scale. All data from the clinical psychiatric examination, interviews with the close informants when possible, as well as psychiatric rating scales and the Schedules for Clinical Assessment in Neuropsychiatry protocol were combined for the final diagnoses of depressive disorders according to the Diagnostic and Statistical Manual of Mental Disorders, revised 3rd edition (DSM-IIIR; APA 1987). Most patients (n=220) were examined by a senior psychiatrist, who also subsequently supervised the afterwards data entry concerning patients examined by a resident psychiatrist (n=37).

The diagnosis of delirium was based on all available information in the patients’ medical records and the nurses’ notes from day 1 to day 7 after admission. A senior psychiatrist with extensive experience as a consulting psychiatrist in a general hospital, evaluated this information structurally according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV; APA 1994). The delirium criteria in DSM-IV were: 1) a disturbance of consciousness and 2) a change in cognition or the development of a perceptual disturbance 3) which develops over a short period of time and fluctuates during the course of the day and 4) which cannot be better accounted for by pre-existing or evolving dementia.

4.5 MAGNETIC RESONANCE IMAGING (III, V, VI)

Figure 2. Different grades of white matter changes according to modified Fazekas Scale: (a) none to mild, (b) moderate, (c) severe.

All patients underwent brain CT at the acute phase. In addition, MRI was performed 3–4 months after the index stroke. MRI was performed with 1.0 T imaging equipment (Siemens Magnetom) (Mäntylä et al. 1999b).

The protocol included transaxial T2, PD and T1-weighted 5 mm thick slices (conventional spin echo technique) and a three dimensional gradient echo sequence.
yielding 65 coronal sections with a thickness of 3 mm. WMC was rated on PD-weighted images as none to mild, moderate or severe according to modified Fazekas scale (Pantoni et al. 2005) which has been previously used in the LADIS study (Leukoaraiosis and Disability in the Elderly; Inzitari et al. 2007). In the none to mild degree of WMC, periventricular lesions included no more than a small cap or thin lining, and in the other WM areas, no more than large focal lesions. In the moderate degree of WMC, periventricular lesions included no more than a large cap and smooth halo, and in the other WM areas, no more than focal confluent lesions. The severe degree of WMC included cases with extending caps or irregular halo in the periventricular area and diffusely confluent lesions or extensive WM changes in other WM areas. Intra- and inter-observer reliabilities for rating basic WMC in periventricular and other WM areas were tested previously and found to be good (weighted kappa 0.72 to 0.95; Mäntylä et al. 1997, Mäntylä et al. 1999a, Mäntylä et al. 1999b). However, we did not retest intra- and inter-observer reliabilities using atlas based assessment of the present follow-up study.

4.6 STROKE SUBTYPE (IV)

The diagnosis of SVD-related lacunar stroke was based on the presence of one of the traditional clinical lacunar syndromes (pure motor stroke, pure sensory stroke, sensorimotor stroke, and ataxic hemiparesis) with no evidence of cerebral cortical dysfunction, and on radiological criteria as follows: normal CT/MRI examination or a relevant brain stem or subcortical hemispheric lesion with a diameter of less than 1.5 cm. A medical history of hypertension and diabetes supported the diagnosis. Cases classified as SVD did not fulfill criteria for LAA and CE. These criteria for a diagnosis of SVD, i.e. lacunar stroke, are consistent with those used in the Trial of Org 10172 in Acute Stroke Treatment (TOAST) (Adams et al. 1993). The exact frequencies of vascular imaging and echocardiography in the cohort are not known, but these frequencies were consistent with the clinical praxis at the time of the initial recruitment, when the availability of investigations did not match those available today.

4.7 SURVIVAL, STROKE RECURRENCE AND CAUSES OF DEATH (I-VI)

Patients were followed until 21 September 2006 using extensive national registers maintained by the National Institute for Health and Welfare. The mean (+-SD) follow up time was 7.5 ± 4.0 years with a range between 0.3 and 12.8 years. The Care Register (previously named the National Hospital Discharge Register) contains
ICD-9 and ICD-10 diagnosis codes for all hospital treatment periods. The ICD-9 codes 433 and 434 and ICD-10 codes I63.0 - I63.9 were considered as ischemic stroke. ICD-9 codes 430 and 431 and ICD-10 codes I60-I61 were considered as hemorrhagic stroke. In addition, survival data and causes of death were obtained from Statistics Finland. Death certificates were reviewed by a forensic pathology specialist and the causes of death were divided in cardiac, brain-associated (differing between infarction, hemorrhage and dementia), infectious, traumatic, cancer or other causes of death. Patients who had died of a brain infarction with no registered hospital treatment were considered to have suffered a fatal recurrent stroke.

4.8 STATISTICAL ANALYSIS

All statistical analyses were carried out using SPSS 15.0 for Windows (SPSS Inc., Chicago, IL) and were performed by Susanna Melkas, MD. The Pearson Chi-square test was used to test dichotomous variables and One-way ANOVA (I, III-VI) or Student’s T-test (II) to test continuous variables. Statistical significance was set at p<0.05.

**Study I.** The effect of dementia diagnosis (any poststroke dementia) was first analyzed using Kaplan-Meier log rank analysis, as was the effect of prestroke cognitive decline and previous stroke among the demented patients. The cumulative hazard function was also applied and according to these analyses, the proportional hazards assumption was met for each parameter included in further models. In Cox regression proportional hazards survival analysis, in the forced entry model (Model 1), the potential predictors were used as covariates (age, sex, years of education, in addition to poststroke dementia). Another model (Model 2) was constructed adding poor Rankin score as a covariate. A third model (Model 3) was constructed adding selected variables from the past medical history as covariates, selecting those variables which were indicated as significant predictors of poor long-term survival in Kaplan-Meier log rank analysis.

**Study II.** The effect of different neuropsychological domains (executive functions, memory, language and visuospatial/constructional abilities), CIND, and copredictors such as global cognitive function (MMSE≤25), education (low education <6 years), and poor modified Rankin score (3–5 vs. 0–2) were first analyzed using Kaplan-Meier log rank analysis. The cumulative hazard function was also used, and according to these analyses, the proportional hazards assumption was met for each parameter included in further models. In Cox regression proportional hazards survival analysis, in the first forced entry model (Model 1), only the demographic background variables were used as covariates (age, sex, years of education). Another model (Model 2) was constructed adding MMSE≤25 and poor modified Rankin score (3–5 vs. 0–2) as clinical covariates.
Subjects and methods

**Study III.** The effects of a depression diagnosis (any poststroke depression) and the severity of depression (major vs. minor) were first analyzed using Kaplan-Meier log rank analysis. Furthermore, the additive effect of executive dysfunction was tested comparing patients with DES and patients with neither depression nor executive dysfunction by means of Kaplan-Meier log rank analysis. The effect of dementia was also tested using Kaplan-Meier log rank analysis. The cumulative hazard function was employed, and according to these analyses, the proportional hazards assumption was met for each parameter included in further models. In Cox regression proportional hazards survival analysis, in the forced entry model, the demographic factors (age, sex, years of education) and the risk factor ‘living alone’ were used as covariates.

**Study IV.** The effect of the SVD subtype of stroke was first analyzed using Kaplan-Meier log rank analysis with all-cause death as endpoint. The effect of SVD was also analyzed using Kaplan-Meier log rank analysis with the endpoints brain-related death, cardiac death and all other deaths. The cumulative hazard function was also applied and according to these analyses, the proportional hazards assumption was met for all other parameters included in further models except for sex and smoking with the endpoint all-cause death, and sex and low education with the endpoint cardiac death. In Cox regression proportional hazards survival analysis with endpoint all-cause death, in the forced entry model (Model 1), demographic factors were used as covariates (age, sex, years of education). Another model (Model 2) was constructed adding stroke severity as a covariate. A third model (Model 3) was constructed adding selected variables from the past medical history as covariates, selecting those variables which were indicated as significant predictors of poor long-term survival in Kaplan-Meier log rank analysis.

**Study V.** Logistic regression analysis was used to detect independent associations between poststroke delirium and different factors. Kaplan-Meier log rank analysis served to assess how poststroke delirium affects long-term survival (endpoint all-cause death). We used the cumulative hazard function and according to these analyses, the proportional hazards assumption was met for all parameters with the endpoint all-cause death. To account for potential confounders and to estimate the predictive value of different factors, we conducted a multivariate Cox regression proportional hazards analysis. In the first forced entry model, demographic factors were used as covariates. In the second forced entry model, we added poststroke dementia as a covariate and in the third model, we added stroke severity. To ensure the reliability of multivariate analysis with regard to the number of patients, we refrained from using additional covariates. We also analyzed the effect of delirium using Kaplan-Meier log rank analysis with the endpoints brain-related death, cardiac death and all other causes of death.

**Study VI.** The association of WMC with demographic and other factors was analyzed with Pearson Chi-square test (dichotomous variables) and one-way ANOVA.
(continuous variables), in addition to binary logistic regression function. The effect of WMC on the time elapsed before the first recurrent stroke was analyzed using Kaplan-Meier log-rank analysis. Life-table function was used to calculate actuarial cumulative recurrence risks and their 95% confidence intervals (CI). Patients who died from other causes besides a recurrent ischemic stroke were considered censored. The cumulative hazard function was applied, and according to these analyses, the proportional hazards assumption was met for each parameter included in further models. To account for potential confounders and to estimate the predictive value of different factors, a multivariate Cox regression proportional hazards analysis was made with forced entry. In the first Cox regression proportional hazards model with the endpoint first recurrent stroke (Model 1), the effect of WMC was analyzed with potential predictors as covariates (age, sex, years of education). A second model was constructed adding selected variables from the past medical history, selecting those variables that associated with stroke recurrence in the Kaplan-Meier analysis. The receiver operating characteristic (ROC) test was used to estimate the area under the curve (AUC) for severe WMC, in order to assess its predictive value for stroke recurrence.
### Table 8: Characteristics of the subjects in sub-studies I-VI.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study IV the whole cohort</th>
<th>Study I</th>
<th>Study II</th>
<th>Study III</th>
<th>Study IV</th>
<th>Study V</th>
<th>Study VI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Valid n</td>
<td>Age (n)</td>
<td>(SD) (%)</td>
<td>Valid n</td>
<td>Age (n)</td>
<td>(SD) (%)</td>
<td>Valid n</td>
</tr>
<tr>
<td>Mean age</td>
<td>486</td>
<td>71.0</td>
<td>(7.7)</td>
<td>451</td>
<td>72.0</td>
<td>(7.7)</td>
<td>409</td>
</tr>
<tr>
<td>Female sex</td>
<td>486</td>
<td>240</td>
<td>49.4%</td>
<td>451</td>
<td>49.0%</td>
<td>409</td>
<td>49.4%</td>
</tr>
<tr>
<td>Low education (≤6yr)</td>
<td>475</td>
<td>151</td>
<td>31.1%</td>
<td>443</td>
<td>30.9%</td>
<td>396</td>
<td>30.6%</td>
</tr>
<tr>
<td>Severe stroke (mRS 3-5)</td>
<td>434</td>
<td>193</td>
<td>44.5%</td>
<td>403</td>
<td>40.4%</td>
<td>409</td>
<td>39.9%</td>
</tr>
<tr>
<td>Smoking (current/former)</td>
<td>482</td>
<td>240</td>
<td>49.8%</td>
<td>450</td>
<td>49.8%</td>
<td>402</td>
<td>49.5%</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>486</td>
<td>98</td>
<td>20.1%</td>
<td>451</td>
<td>20.0%</td>
<td>409</td>
<td>18.8%</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>486</td>
<td>93</td>
<td>19.1%</td>
<td>451</td>
<td>19.1%</td>
<td>409</td>
<td>18.8%</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>485</td>
<td>107</td>
<td>22.1%</td>
<td>450</td>
<td>21.6%</td>
<td>408</td>
<td>21.3%</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>485</td>
<td>98</td>
<td>20.2%</td>
<td>450</td>
<td>18.9%</td>
<td>408</td>
<td>19.6%</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>486</td>
<td>230</td>
<td>47.3%</td>
<td>451</td>
<td>47.5%</td>
<td>409</td>
<td>48.9%</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>486</td>
<td>58</td>
<td>11.9%</td>
<td>451</td>
<td>11.8%</td>
<td>409</td>
<td>11.1%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>486</td>
<td>120</td>
<td>24.7%</td>
<td>451</td>
<td>24.6%</td>
<td>409</td>
<td>23.2%</td>
</tr>
</tbody>
</table>

mRS, modified Rankin Scale. SD, standard deviation.
5 RESULTS

The basic demographics of the six sub-studies are shown in Table 8. The results of the univariate analysis (Kaplan Meier log rank analysis and Lifetable analysis) are summarized in Table 9 and the results of multivariate analysis in Table 10.

Table 9. Kaplan-Meier analysis on the association of the manifestations of small-vessel disease and survival (I-V), and life-table analysis on stroke recurrence (VI).

<table>
<thead>
<tr>
<th>Sub-study</th>
<th>Follow-up</th>
<th>Endpoint</th>
<th>Median survival until end point, (95% confidence interval), p-value.</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Dementia</td>
<td>12 years</td>
<td>All-cause death</td>
<td>No dementia 8.8 years (7.8 to 9.9), any poststroke dementia 5.1 years (4.1 to 6.0), p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Without prestroke cognitive decline 5.8 years (4.8-6.9), with prestroke cognitive decline 3.8 years (2.2 to 5.4), p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>First ever stroke 5.4 years (4.6 to 6.2), at least one previous stroke 4.5 (2.9 to 6.1), p=0.676</td>
</tr>
<tr>
<td>II Cognitive deficits</td>
<td>12 years</td>
<td>All-cause death</td>
<td>Without executive dysfunction 10.1 years (8.7 to 11.4), with executive dysfunction 5.8 years (4.7 to 7.0), p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Without memory deficit 9.3 years (7.9 to 10.7), with memory deficit 6.8 years (5.3 to 8.3), p=0.009</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Without language deficit 8.6 years (7.7 to 9.4), with language deficit 5.3 years (3.8 to 6.9), p=0.004</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Without visuospatial deficit 10.1 years (8.5 to 11.7), with visuospatial deficit 5.6 years (4.6 to 6.7), p&lt;0.001</td>
</tr>
<tr>
<td>III Depression</td>
<td>12 years</td>
<td>All-cause death</td>
<td>No depression 8.3 years (6.9 to 9.7), any poststroke depression 8.7 years (6.4-11.1), p=0.866</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No depression nor executive dysfunction 10.3 years (8.6 to 12.1), DES 6.6. (5.1-8.1), p=0.014</td>
</tr>
<tr>
<td>IV SVD subtype of stroke</td>
<td>12 years</td>
<td>All-cause death</td>
<td>Non-SVD subtype 7.9 years (7.1 to 8.7), SVD subtype 4.3 years (2.9 to 5.6), p&lt;0.001</td>
</tr>
<tr>
<td>V Delirium</td>
<td>10 years</td>
<td>All-cause death</td>
<td>No delirium 9.1 years (7.9 to 10.2), poststroke delirium 6.1 years (4.8 to 7.4) p=0.034</td>
</tr>
<tr>
<td>VI Severe WMC</td>
<td>5 years</td>
<td>Recurrent ischemic stroke</td>
<td>None to moderate WMC 24.5% (23.8 to 25.2), severe WMC 39.1% (38.1 to 40.1), p=0.004</td>
</tr>
</tbody>
</table>

SVD, small-vessel disease. DES, depression-executive dysfunction syndrome. WMC, white matter changes.
5 Results

Table 10. Cox regression analysis on the association of the manifestations of small-vessel disease and survival (I–V), and stroke recurrence (VI).

<table>
<thead>
<tr>
<th>Sub-study</th>
<th>HR</th>
<th>95% confidence interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Dementia</td>
<td>1.53</td>
<td>1.15 to 2.04</td>
<td>0.003</td>
</tr>
<tr>
<td>II Cognitive deficits:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Executive dysfunction</td>
<td>1.33</td>
<td>1.01 to 1.74</td>
<td>0.040</td>
</tr>
<tr>
<td>Memory deficit</td>
<td>1.20</td>
<td>0.92 to 1.57</td>
<td>0.182</td>
</tr>
<tr>
<td>Language deficit</td>
<td>1.11</td>
<td>0.82 to 1.48</td>
<td>0.509</td>
</tr>
<tr>
<td>Visuospatial deficit</td>
<td>1.53</td>
<td>1.14 to 2.04</td>
<td>0.004</td>
</tr>
<tr>
<td>III DES</td>
<td>1.63</td>
<td>1.05 to 2.52</td>
<td>0.031</td>
</tr>
<tr>
<td>IV SVD subtype of stroke</td>
<td>1.60</td>
<td>1.06 to 2.41</td>
<td>0.025</td>
</tr>
<tr>
<td>V Delirium</td>
<td>1.32</td>
<td>0.90 to 1.95</td>
<td>0.158</td>
</tr>
<tr>
<td>VI Severe WMC</td>
<td>1.80</td>
<td>1.11 to 2.95</td>
<td>0.018</td>
</tr>
</tbody>
</table>

HR, hazard ratio. DES, depression-executive dysfunction syndrome. SVD, small-vessel disease. WMC, white matter changes.

5.1 FACTORS AFFECTING ISCHEMIC STROKE SURVIVAL

5.1.1 POSTSTROKE DEMENTIA (I)

In Kaplan-Meier log rank analysis, patients with dementia 3 months after stroke, i.e. with any poststroke dementia (n=115/451, 25.5%), had shorter median survival after stroke than patients without dementia (n=336/451, 74.5%; p<0.001; Table 9). Among the demented stroke patients, those who had had a prestroke cognitive decline (n=37/115, 32.2%) had shorter median survival than those without prestroke cognitive decline (n=78/115, 67.8%; p<0.001). Furthermore, among the demented patients there was no significant difference between the survival of patients with their first-ever stroke (n=90/115, 78.3%) and those with at least one previous stroke (n=25/115, 21.7%; p=0.676; Table 9).

To account for potential confounders and to estimate the predictive value of different factors, a multivariate Cox regression proportional hazards analysis was carried in three steps, Model 1-3 as described above in Statistical analyses section. In Model 3 we added selected variables from the past medical history indicated as significant predictors of poor long-term survival using Kaplan-Meier log rank analysis. These predictors were smoking, myocardial infarction, cardiac failure, cardiac arrhythmia and atrial fibrillation (all with p<0.05), with peripheral arterial disease being of borderline significance (p=0.058).

In Model 1, poststroke dementia and advanced age were independent predictors of poor longterm survival (p<0.001). Adding stroke severity to the model, poststroke dementia remained associated with increased risk of death (p=0.002), in addition to advanced age (p=0.002) and more severe stroke as defined with mRS score 3-5 (p<0.001). Finally in Model 3, advanced age (HR 1.07, CI 1.05-1.09, p<0.001), mRS
3-5 (HR 1.91, CI 1.47-2.48, p<0.001), smoking (HR 1.35, CI 1.02-1.77, p=0.035), cardiac failure (HR 1.61, CI 1.18-2.19, p=0.003) and atrial fibrillation (HR 1.89, CI 1.05-3.42, p=0.035) remained as independent predictors of poor long-term survival in addition to poststroke dementia (HR 1.53, CI 1.15-2.04, p=0.003; Table 10).

5.1.2 POSTSTROKE COGNITIVE IMPAIRMENT (II)

In Kaplan-Meier log rank analysis, deficits in executive functions (n=176, 48.2%), memory (n=227, 59.9%), language (n=114, 28.9%) and visuospatial/constructional abilities (n=216, 55.2%) predicted poor survival (Table 9). Furthermore, low education (≤6 years) (n=151, 31.8%) (6.4 years, CI 5.4−7.3, vs. 8.2 years, CI 7.1−9.1 years, p=0.003), MMSE ≤25 (n=138, 30.5%) (4.4 years, CI 3.7−5.1, vs. 9.3 years, CI 8.3−10.4, p<0.001) and mRS 3–5 (n=194, 39.9%) (3.9 years, CI 4.2−5.6, vs. 9.7 years, CI 8.5−10.9, p<0.001) predicted poor poststroke survival.

In Cox regression proportional hazards analysis (Model 1, including age, sex and years of education), deficits in executive functions, memory, language and visuospatial/constructional abilities remained as significant predictors of poor poststroke survival (Table 10). Deficits in executive functions and visuospatial/constructional abilities remained as significant predictors after the addition of MMSE≤25 and mRS 3–5 as covariates (Model 2; table 10). MMSE≤25 and mRS 3–5 predicted poor survival in all the models. To further explore the role of cognitive impairment, we analyzed the effect of cognitive impairment no dementia (CIND) on poststroke survival. In this population (n=284), CIND (n=212, 74.6%) (7.9 years, CI 7.4−8.5, vs 9.7 years, CI 8.8−10.6, p=0.003) was a predictor of poor poststroke survival when compared with patients with no cognitive impairment in any of the assessed domains. In Cox regression proportional hazard analysis with age, sex and years of education as covariates, CIND remained an independent predictor of survival (HR 1.63, CI 1.12−2.39, p=0.012).

5.1.3 POSTSTROKE DEPRESSION AND DEPRESSION-EXECUTIVE DYSFUNCTION SYNDROME (DES) (III)

In Kaplan-Meier log rank analysis, patients with depression 3 months after stroke—i.e. with any poststroke depression (n=99/257, 38.5%)—had similar median survival after stroke as patients without depression (p=0.866; Table 9). Separating major depression from minor, there was also no significant difference in median survival between patients with major depression (n=65/257, 25.3%, 8.1 years, CI 7.1−9.1) and those without depression (p=0.633).

Patients with poststroke DES (n=47/257, 18.3%) had a shorter median survival
than patients with neither depression nor executive dysfunction (n=91/257; p=0.014; Table 9). Comparison between all patients with executive dysfunction (n=114) and patients without it (n=143), not regarding depressive status, showed that executive dysfunction in itself was associated with poor poststroke survival (6.4 years, CI 5.4–7.3; vs. 10.6 years, CI 9.3–11.9; p<0.001). Comparison between the four groups represented by the presence or absence of depression and executive dysfunction showed that patients with only executive dysfunction and those with DES had a similarly poor survival. An interaction term combining depression and executive dysfunction was created. When this term was used in a multivariate analysis adjusted for covariates (age, sex, low education, living alone and dementia), the hazard ratio for the interaction did not reach level of significance (HR 1.18, CI 0.81–1.73; p=0.384).

Further, comparison between all patients with dementia (n=57) and patients without it (n=200), not regarding depression, showed that dementia in itself was associated with poor poststroke survival (6.4 years, CI 5.3–7.4; vs. 9.4 years, CI 7.7–11.1; p=0.008 using Kaplan-Meier log rank analysis).

3-year and 5-year follow-ups were simulated in order to investigate if depression is a predictor of earlier poststroke death. No association was found between poststroke depression and survival neither after 3 years nor after 5 years (data not shown).

To account for potential confounders and to estimate the predictive value of different factors in the subpopulation including patients with DES and those with neither depression nor executive dysfunction, a multivariate Cox regression proportional hazards analysis was made with forced entry. Poststroke DES (p=0.031) and advanced age were independent predictors of poor long-term survival. Dementia did not remain an independent predictor in this model.

5.1.4 SVD SUBTYPE OF STROKE, LACUNAR STROKE (IV)

The stroke etiology was small-vessel disease (SVD) in 63 patients (13.0%) and non-SVD in 423 patients (87%). Median survival was 4.3 years for SVD and 7.9 years for non-SVD (p<0.001; Table 9).

In the first Cox regression proportional hazards model, SVD (p<0.001), advanced age (p<0.001), and male sex (p=0.012) were associated with poor survival. When stroke severity was added to the model (Model 2), SVD remained associated with increased risk of death (p<0.001), in addition to advanced age and severe stroke (p<0.001 for both). In Model 3, SVD (p=0.025; Table 10), advanced age (p<0.001), severe stroke (p<0.001), smoking (p=0.007), and cardiac failure (p=0.005) were all associated with poor long-term survival.
Previous stroke was not a predictor of mortality in the present study. Of the 63 patients with SVD, nine (14.3%) had had a previous stroke, whereas the corresponding proportion in the whole cohort was 98/486 (20.2%). Instead, more severe stroke as defined with mRS 3-5 remained associated with mortality after adjusting for demographic factors and risk factors.

5.1.5 POSTSTROKE DELIRIUM (V)

Acute stage delirium after stroke (i.e., from day 1 to day 7 after admission) was diagnosed in 19.0% of the patients (50/263). Patients with poststroke delirium seemed to be more likely to have a low level of education (40.0% vs. 25.6%, and p=0.043) and had more often suffered a severe stroke (65.9% vs. 25.4%, p<0.001) than did patients without delirium. The patients with delirium were more likely to have experienced prestroke cognitive decline than those without delirium (28.0% vs. 4.2%, p<0.001). Furthermore, poststroke dementia also occurred significantly more frequently in patients with delirium than in those without it (50.0% vs. 16.9%, p<0.001). Logistic regression analysis verified the association with all other mentioned factors but not with low education.

In the Kaplan-Meier log rank analysis, patients with poststroke delirium had shorter median survival than did patients without delirium (p=0.034; Table 9). In Model 1 of the multivariate Cox regression proportional hazards analysis, only advanced age was associated with poor long-term survival. In Model 2, poststroke dementia at 3 months was added as a covariate and appeared to be associated with poor survival, in addition to advanced age. In Model 3, when mRS 3-5 was added as a covariate, only mRS 3-5 and advanced age were associated with poor survival.

5.2 CAUSES OF POSTSTROKE DEATH (I-V)

Study I. A brain-associated cause of death in general (p=0.002), and brain infarction in particular (p=0.001) were associated with poststroke dementia in the univariate analysis of causes of death. In Kaplan-Meier analysis with brain-associated death as the endpoint, patients with poststroke dementia had a shorter survival (6.8 years, CI 4.6–8.9) compared to patients without dementia (11.1 years, CI 10.2–11.9, p<0.001). In multivariate Cox regression analysis with a brain-associated cause of death as the endpoint, adding covariates in three steps, poststroke dementia remained an independent predictor of poor survival (p<0.001), in addition to advanced age (p<0.001) and mRS 3-5 (p=0.001).

Study II. The probability of dying due to cardiac causes alone showed no association with deficits in any of the cognitive domains according to the univariate
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analysis using the Kaplan-Meier log rank test. Death due to brain-related causes, on the other hand, was more likely in those with deficits in executive functions (p=0.019), language (p=0.001) and visuospatial/constructional abilities (p<0.001). No associations were found between the cognitive domains and infectious, traumatic, or other causes of death.

**Study III.** A brain-related cause of death, including infarction, hemorrhage and dementia, was associated with DES in the univariate analysis (p=0.007), but the low number of patients at risk after 10 years limits the significance of this result. Therefore, no multivariate analysis was performed with brain-related death as the endpoint. An analysis of the difference in the causes of death between all patients with executive dysfunction and those without it (N=257, total of 168 deaths) showed the same trends as between patients with DES and those with neither depression nor executive dysfunction (N=138, total of 87 deaths).

**Study IV.** SVD was associated with a cardiac cause of death, but not with brain-related or other causes of death. In the Kaplan-Meier analysis where cardiac-associated death was the endpoint, patients with SVD had a shorter survival (8.2 years, CI 5.7–10.7) than those with other subtype (10.4 years, CI 9.0–11.8, p=0.002). In multivariate Cox regression proportional hazards models with cardiac death as the endpoint, SVD was associated with poor survival (p=0.021) even when stroke severity (mRS 3-5) was accounted for.

**Study V.** Brain infarction as the cause of death was associated with poststroke delirium in the univariate analysis (p=0.006). Other causes of death were not associated with poststroke delirium (other brain-related, cardiac, or other causes of death). Multivariate analysis of the causes of death could not be carried out due to the small number of cases in each category.

### 5.3 FACTORS AFFECTING ISCHEMIC STROKE RECURRENTNESS: WHITE MATTER CHANGES (VI)

None to moderate WMC appeared in 49.4% (158/320) of the patients, and severe WMC was found in 50.6% (162/320) of the patients. Severe WMC was associated with advanced age and diabetes. Logistic regression analysis verified the association with advanced age only.

At least one recurrent ischemic stroke, non-fatal or fatal, was diagnosed in 76 (23.8%) patients at 5 years and in 127 (39.7%) patients at 12 years. Hemorrhagic stroke (intracerebral hemorrhage in all cases) occurred in 5 patients as the first recurrent event and in 4 patients after a recurrent ischemic event. In the subsequent analysis, we concentrated on the recurrence of ischemic stroke, due to the low number of hemorrhagic strokes that would not have enabled a separate analysis.
The cumulative one-year recurrence risk according to life table analysis was 8.0% (CI 7.6%–8.4%) for patients with none to moderate WMC and 18.6% (CI 18.1%–19.1%) for patients with severe WMC. At 3 years the recurrence risk was 14.4% (CI 13.9%–14.9%) for none to moderate WMC and 29.1% (CI 28.4%–29.8%) for severe WMC; at 5 years 24.5% (CI 23.8%–25.2%) for none to moderate WMC and 39.1% (CI 38.1%–40.1%) for severe WMC; and at seven years 35.0% (CI 34.1%–35.9%) for none to moderate WMC and 44.3% (CI 43.1%–45.5%) for severe WMC. Correspondingly, cumulative 12-year recurrence risk was 48.1% (CI 45.5%–50.7%) for patients with none to moderate WMC and 60.9% (CI 56.7%–65.1%) for patients with severe WMC. The recurrence risk was significantly higher for patients with severe WMC than for those with none to moderate WMC (log rank test, p=0.004).

Independent predictors of recurrent stroke at 5 years were severe WMC (p=0.018; table 10), atrial fibrillation (HR 1.81, CI 1.09–3.02; p=0.022), hypertension (HR 1.69, CI 1.05–2.71; p=0.031) and peripheral arterial disease (HR 1.89, CI 1.06–3.38; p=0.031) (Table 3). At 7 years, increasing age (HR 1.04, CI 1.01–1.07; p=0.003) and low education (HR 1.53, CI 1.06–2.23; p=0.025) were independent predictors of recurrent stroke. At 12 years, only increasing age (HR 1.04, CI 1.02–1.07; p=0.001) remained independently associated with the risk of recurrent stroke.

In receiver operating characteristic (ROC) analysis, the area under the curve for WMC severity was 0.58 (CI 0.51–0.65) for the prediction of stroke recurrence within 5 years.
6 DISCUSSION

6.1 THE EFFECT OF DEMENTIA AND COGNITIVE IMPAIRMENT ON POSTSTROKE SURVIVAL (I, II)

According to our results, poststroke dementia and mild cognitive impairment relate to poor long-term survival poststroke. Prestroke cognitive decline seems to have an additional negative influence on survival in patients with poststroke dementia, but previous stroke does not seem to affect survival. Deficits in executive functions as well as visuospatial and constructional abilities, in particular, predict poor outcome independently of global cognitive decline and the severity of stroke.

The proportion of patients with poststroke dementia was 26% in our cohort, and the proportion of patients with cognitive deficits in different domains varied in between 29%–60%. Previously Tatemichi et al. (1994) and Desmond et al. (2002) have also found a prevalence of 26% for poststroke dementia in corresponding hospital-based populations, and in a cohort by Barba et al. (2002), also including patients with intracranial hemorrhage, the prevalence was 31%. The prevalence of poststroke cognitive deficits has not been studied in detail previously. The proportion of patients with a low MMSE score in Study II (29%) is in line with a previous study of hospitalized patients (House et al. 2001).

Poststroke dementia has previously been associated with poor long-term survival by both Tatemichi et al. (1994) and Desmond et al. (2002). The effect of poststroke dementia in our study was somewhat weaker than was found in the previous studies: the hazard ratio was 1.5 in the present study, while the risk ratio in the study by Tatemichi et al. was 3.1 and the risk ratio in the study by Desmond and co-workers was 2.4, all of which are after adjusting for major confounders.

In line with our finding, a negative influence for prestroke dementia on poststroke survival was reported in two studies (Barba et al. 2002, Appelros et al. 2005), whereas the study by Hénon and colleagues (2003a) did not confirm this finding. Previous stroke did not have an effect on survival in our cohort (4.5 years with previous stroke vs. 5.4 years with first-ever stroke) where 21.7% of patients had suffered a previous stroke. This influence has not been analyzed separately in other studies.

We found an association between poststroke dementia and a brain-associated cause of death, more specifically brain infarction, which is in contrast with two previous studies where the causes of death did not differ between the demented and non-demented patients (Desmond et al. 2002, Hénon et al. 2003a). On the other
hand, there was no specific association between poststroke dementia and dementia as a cause of death in our study. This finding is probably linked to the general reluctance to cite dementia as the primary cause of death, aside from when there is clear evidence for primarily degenerative progressive dementia, with Alzheimer’s disease in particular. Fatal progression of vascular dementia is often associated with stroke recurrence, and in such cases the cause of death is brain infarction.

In line with the findings regarding dementia, global MMSE and CIND were also associated with survival in our cohort. Previous documentation on the influence of MMSE is diverging—three studies with up to 4 years’ follow-up showed a similar association (Patel et al. 2002, Friedman, 1991, House et al. 2001), whereas two short 1-year studies demonstrate that MMSE is not an independent predictor of survival (Thommenessen et al. 1999, Altieri et al. 2002). CIND has been related to impaired survival in studies of community-based populations where stroke has not been regarded (Ingles et al. 2003, Tuokko et al. 2003, Hsiung et al. 2006). Our results of CIND as an independent predictor of poor poststroke survival in a specified poststroke population are new and of clinical significance. The recognition of CIND might alert clinicians to schedule more strict and accurate follow-up.

Furthermore, we found that impairment in major cognitive domains related to poor poststroke survival. When controlling for the effect of global cognitive decline (MMSE≤25) and severity of stroke, only executive functions as well as visuospatial and constructional abilities, which are executing-related functions, remained independent correlates of poor survival. As far as we know, there are no previous studies with detailed neuropsychological examinations to compare this result with. The executive syndrome relates to SVD lesions (WMC and lacunar) attacking the pre-frontal subcortical circuit — i.e. it is an expression of the role of small-vessel executive network brain concept (Erkinjuntti 2000; Román 2002).

Given that cognitive decline, both manifest dementia and less severe stages of cognitive impairment, significantly worsens outcome after stroke, it is important to recognize patients with these conditions in order to offer them optimum comprehensive care.

6.2 THE EFFECT OF DEPRESSION AND DELIRIUM ON LONG-TERM SURVIVAL (III, V)

The present results indicate that in poststroke depression, depression-executive dysfunction syndrome (DES) is the predictor of poor long-term survival rather than depression in itself. In addition, delirium is a frequent poststroke complication associated with an elevated risk of dementia at 3 months poststroke, but it does not independently relate to mortality.
In our study the prevalence of any poststroke depression (major or minor) was 39% and of major depression 25% at the 3-month assessment. The prevalence apparently fluctuates as a function of time: in a population-based study by Åström et al. (1993), the prevalence of major depression was 25% immediately after stroke, 31% at 3 months, 16% at 12 months, 19% at 2 years and 29% at 3 years. In a hospital-based study by Morris et al. with an assessment 1-3 weeks poststroke, 41% of the subjects had any depression, 22% had major depression and 19% had minor depression. Furthermore, Burvill et al. (1995) found that 41% of the patients who were depressed 4 months after stroke were still depressed at 1 year. All in all, according to a review the mean prevalence of poststroke major depression in hospital-based studies has been 19% and that of poststroke minor depression 30% (Robinson 2006).

According to our results, survival in poststroke depression is determined by concurrent executive dysfunction rather than depression in itself. In previous documentation, the influence of depression has seemed controversial, perhaps because DES has been disregarded. We also found, in accordance with Study II, that executive dysfunction is a strong predictor of poor poststroke outcome.

Even though depression does not seem to have an additive effect on survival from the executive dysfunction viewpoint, we would like to emphasize the clinical importance of DES in the care of elderly stroke patients. From the therapeutic viewpoint DES is an important category within both depression and executive dysfunction, and disregarding DES might both prevent the optimum care of these patients and distort the analysis of poststroke outcome.

One in five patients in our cohort developed poststroke delirium, which is well in line with the prevalence rates of poststroke delirium reported in previous studies (McManus et al. 2007). We found that poststroke delirium was associated with a higher risk for dementia at 3 months poststroke. Risk factors for poststroke delirium were low education, prestroke cognitive decline, and stroke severity. Advanced age and stroke severity were associated with increased long-term mortality in patients with poststroke delirium.

In accordance with our study, prestroke cognitive decline (Gustafson et al. 1991, Hénon et al. 1999) and stroke severity (Gustafson et al. 1991, Hénon et al. 1999, Sheng et al. 2006, McManus et al. 2009) have previously been related as risk factors to poststroke delirium. Low education has been identified as a risk factor in a more heterogeneous study population (Jones et al. 2006), but not in poststroke studies (Hénon et al. 1999, Caeiro et al. 2004). The frequency of dementia after poststroke delirium has not been investigated in previous studies. However, Hénon et al. (1999) found that the MMSE score at 6 months was significantly lower in patients with poststroke delirium than in patients without it. Bearing in mind the present results, poststroke delirium can be seen as an indicator of poor brain reserve capacity, associating with an elevated risk of dementia at 3 months poststroke.
6.3 THE EFFECT OF SVD SUBTYPE OF STROKE, LACUNAR STROKE ON LONG-TERM SURVIVAL (IV)

Although stroke due to SVD may not appear as severe in the acute phase and has favorable short-term outcome, the outcome for patients suffering the SVD subtype of stroke—i.e. lacunar stroke syndrome—seems to be worse in comparison to other stroke subtypes when patients are followed for a long period. Our results also show that acute index stroke attributable to SVD is associated with higher risk for cardiac death than other stroke subtypes.

The present results are in accordance with the study by Staaf et al. (2001), where the prognosis for SVD became less favorable in long-term follow-up than in the short-term: the risk of death after pure motor stroke was similar to that of the general population during the first 5 years, but beyond that point in time, the risk increased by 10%–15% when compared with the general population.

We suggest that cerebral SVD belongs to a larger group of SVD-related end-organ manifestations, similar to what is seen in the heart, the kidneys, the musculature and the retina. For example the high prevalence of AF among our SVD patients reflects the fact that heart muscle small-vessel involvement leading to atrial enlargement is a factor behind atrial fibrillation. More evidence on the close relation between cerebral and systemic SVD comes from a study of our cohort, where kidney function as reflected by the estimated glomerular filtration rate (eGFR) associated with increased poststroke mortality (Oksala et al. 2010). Similar association between kidney function and poor outcome has been found in a cohort of young stroke patients (Putaala et al. 2011c).

6.4 CAUSES OF DEATH IN STROKE PATIENTS WITH DIFFERENT MANIFESTATIONS OF CEREBRAL SMALL-VESSEL DISEASE (I-V)

The causes of death were addressed in our study as a by-product of survival data. According to our results both poststroke dementia and deficits in specific cognitive domains (executive functions, language and visuospatial/constructional abilities) are associated with brain-related causes of death in a 12-year follow-up. Poststroke DES and delirium also seem to be associated with brain-related causes of death, but the low number of patients after 10 years limits the significance of these results. Prior long-term studies have not investigated cause-specific mortality in relation to these conditions. The SVD subtype of stroke is associated with cardiac cause of death in our study, in accordance with previous documentation as reviewed by Norrving (2003).
6.5 THE EFFECT OF WHITE MATTER CHANGES, SURROGATE OF SMALL-VESSEL DISEASE ON STROKE RECURRENCE (VI)

We found that severe WMC relates independently to an increased risk of stroke recurrence at 5 years. The severity of WMC can be considered as an SVD marker, an SVD surrogate that summarizes the effects of several classical risk factors on the small-vessel brain network and can therefore be used to estimate a person’s 5-year risk for developing a recurrent ischemic stroke after the first-ever ischemic stroke.

In the present study of patients aged 55 to 85 years with mean age of 70.8 years, the influence of increasing age on stroke recurrence became more dominant as the follow-up became longer. Accordingly, this may explain why the association of WMC with recurrent stroke only extended to five years in our study. Another explanation may be a lack of power in the study as the follow-up becomes longer.

A score based on the severity of WMC could have clinical utility in the risk stratification of stroke recurrence in a similar manner as the Framingham Risk Score (FRS), for example, is used in estimating the risk of developing cardiovascular disease (CVD), i.e., coronary heart disease (CHD) or stroke (Third Report of the NCEP 2002). According to the ROC analysis, the predictive value of WMC is comparable to that of FRS. As an example, in a larger cohort of 5,128 men with no prior CVD, the AUC for FRS in discriminating the combined cases of CHD, stroke and diabetes was 0.67 (95% CI 0.65–0.69) (Wannamethee et al. 2005). However, larger study populations are needed to estimate the stroke recurrence risk according to three grades of WMC instead of the two that we used.

6.6 METHODOLOGICAL CONSIDERATIONS (I-VI)

All sub-studies were conducted as part of the Helsinki Stroke Aging Memory -study, with the same cohort of 486 ischemic stroke patients admitted to hospital. The strengths of the study include the well-defined, large and consecutive cohort and the long-term follow-up (12 years). The data on survival and causes of death is comprehensive with a negligible number of unresolved deaths.

The patients underwent clinical, neuroradiological, neuropsychological and psychiatric examinations. Well-established criteria were used for diagnosis which makes our results easy to compare with previous documentation. A diagnosis of dementia was based on DSM-III, depression on DSM-IIIR and delirium on DSM-IV. Cognitive deficits were evaluated using comprehensive standardized neuropsychological tests. The diagnosis of the SVD subtype of stroke was based on the criteria used in the Trial of Org 10172 in Acute Stroke Treatment (TOAST) (Adams et al. 1993). The severity of WMC was evaluated according to the modified
Fazekas rating scale (Pantoni et al. 2005), which has been previously used in the large LADIS study (Inzitari et al. 2007).

However, the definition of prestroke cognitive decline in the Studies I and V was based on detailed clinical history instead of more standard assessment with the Informant Questionnaire on Cognitive Decline in the Elderly (Barba et al. 2002, Hénon et al. 2003a). The use of alcohol, a risk factor for depression and delirium, has not been surveyed accurately enough to use it as a covariate in Studies III and V.

A potential limitation in our cohort is the possibility of selection bias, because the cohort was formed 3 months after the index stroke. Attrition over 3 months may limit the generalizability of the results. Therefore we retrospectively obtained additional data from an independent organization on stroke-related deaths in the Helsinki University Central Hospital district during the period in which we collected our data. In this retrospective data, up to 64% of stroke-related deaths occurred in women. Although the proportions of the sexes in our cohort were more equal, this finding suggests that some women may have died before hospital assessment at 3 months.

The official cause of death has been demonstrated to be an accurate means of evaluating disease-specific mortality in Finland (Mäkinen et al. 2008). The determination of cause of death based on autopsy approximately in 30% of all deaths in Finland in the past two decades (www.tilastokeskus.fi) which is a rather high figure when compared to other European countries. In addition, the death certificates of all the deceased, whether subjected to autopsy or not, are reviewed by the district forensic physician. Our follow-up also comprised a review of the death certificate data by a forensic pathology specialist. A potential limitation in our study is that approximately 10%−15% of stroke diagnoses may be incorrect in Scandinavian national registers—there are factors that can lead both to overestimation and underestimation of the frequency of stroke diagnosis (Leppälä et al. 1999). However, the Care register data are comprehensive with no missing cases.

6.7 GENERAL DISCUSSION AND FUTURE IMPLICATIONS

The cerebral SVD perspective to poststroke survival and ischemic stroke recurrence confirms that the cognitive and neuropsychiatric consequences of stroke are as important prognostic factors as motor consequences. Different manifestations of cerebral SVD associate with increased long-term mortality and ischemic stroke recurrence.

SVD is a systemic disease that progresses in silence and has disabling and life-threatening influences mainly on the brain, the heart and the kidneys. A practical marker of SVD would help clinicians to find the individuals with elevated risk and
to offer them optimum care. The presence of cerebral SVD is also investigated as a prognostic factor for example for the benefits of carotid endarterectomy.

According to our results, the severity of WMC influences poststroke prognosis regarding stroke recurrence. A previous study with the same cohort showed association between WMC and poststroke mortality (Oksala et al. 2009). As mentioned above, also kidney function as reflected by estimated glomerular filtration rate (eGFR) associated with increased poststroke mortality in this cohort (Oksala et al. 2010). We suggest that both eGFR and WMC can be used as markers of SVD and as indicators for poststroke prognosis.

Future studies will further elucidate the association between cerebral SVD and major aspects of poststroke morbidity – for example hip fractures, cardiac disease and psychiatric morbidity.

At present, therapy of cerebral SVD does not differ from the classical primary or secondary prevention of stroke. However, as more knowledge about the true nature of cerebral SVD is emerging, the search for new therapeutic targets and rehabilitation strategies is accelerating.
7 CONCLUSIONS AND SUMMARY

Cerebral SVD is recognized as an important cause of dementia and cognitive impairment. Poststroke dementia is independently associated with increased risk of long-term mortality. Cognitive impairment no dementia, i.e. mild vascular cognitive impairment is related to poor long-term survival poststroke. In particular deficits in executive functions, which are critical for the small-vessel network brain, predict poor outcome.

Depression and delirium are frequent poststroke complications, but they do not independently relate to mortality. However, depression-executive dysfunction syndrome (DES) is associated with poor poststroke survival. Delirium is associated with an elevated risk for dementia at three months poststroke.

Acute index stroke attributable to SVD—i.e. lacunar stroke—is associated with poorer long-term survival and higher risk for cardiac death than other stroke subtypes. Severe WMC, a surrogate of SVD, is independently related with increased ischemic stroke recurrence risk at five years.

In summary, SVD is an important determinant of poststroke mortality and ischemic stroke recurrence, regardless of whether it is the cause of the index stroke or a concurrent condition to other etiology. More knowledge about the true nature of cerebral SVD is emerging, which will hopefully reveal new avenues for preventing and treating SVD, in addition to improving its prognosis.
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