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Vascular Risk Factors in the Very Old with the Emphasis on Mortality and Cognition

Doctoral dissertation

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ABSTRACT

As the population ages, dementia and vascular diseases are becoming major problems. Since there is no cure for the dementia syndrome, its prevention is even more important.
The purpose of this study was to evaluate the most common vascular risk factors and their influence on dementia and mortality in the very old. We focused especially on blood pressure and its association with mortality, atrial fibrillation and its association with stroke and brain pathology and common vascular risk factors such as diabetes mellitus, blood pressure, lipids, homocysteine and their association with incident dementia. In one study, we evaluated the association between the APOE allele, blood pressure and cardiac arrhythmias.
This study was a population based longitudinal study and the study population consisted of all residents whether living in institutions or at home in the City of Vantaa and aged 85 years or over (N=601) on April 1st, 1991. The final baseline cohort included 553 (92%) individuals. There were three follow-up evaluations which were conducted in 1994, 1996, and 1999.
The subjects were examined by a neurologist and the diagnosis of dementia was made based on clinical examination, MMSE and DSM-III-R criteria. We also evaluated SPMSQ, CDR, ADL, and IADL. Blood pressure measurements were taken in a standardized manner and resting ECG or short ambulatory holter ECG were recorded and APOE genotyping was made. Over half of the baseline study population was autopsied by 31st March 2001.
The main results in our study were that low systolic blood pressure (<140 mmHg) was associated with increased mortality. Atrial fibrillation associated with baseline and macroscopical stroke. High blood pressure and education seemed to protect from dementia and diabetes mellitus was associated with incident dementia. APOE ε4 associated with dementia, though this association disappeared when adding neuropathological factors into the model.
This study confirms that in this very special old population some conventional vascular risk factors such as blood pressure are not as clear a risk factor for mortality as in younger populations. It seems that the role of APOE genotype and most vascular risk factors may weaken with age. However, this study showed that the treatment of atrial fibrillation is most crucial in the prevention of stroke and in that also of dementia. The influence of vascular risk factors on dementia in this very old age-group is probably mediated through cerebrovascular morbidity and the prevention of stroke and diabetes is highly important also in prevention of cognitive decline.
Very old people have an extremely fragile cerebrovascular system and their compensation mechanisms to combat vascular brain damage are weak. However, in epidemiological studies they are not comparable with younger people with respect to vascular risk factors of dementia or mortality. Potential benefits of risk factor treatments, on the other hand, must be analyzed in randomized clinical studies.

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Medical Subject Headings: Age Factors; Aged, 80 and over; Aging; Apolipoproteins E; Atrial fibrillation; Blood Pressure; Brain; Dementia; Diabetes Mellitus; Finland; Homocysteine; Lipids; Mortality; Risk Factors; Stroke; Urban population

To Kaj and Väinö

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Espoo, November 2009

Sari Rastas

ABBREVIATIONS

AD	Alzheimer’s disease
ADL	Active daily living
AF	Atrial fibrillation
APOE	Apolipoprotein E (gene)
ApoE	Apolipoprotein E (protein)
A-V block	Atrio-ventricular block
BP	Blood pressure
CAA	Cerebral amyloid angiopathy
CADASIL	cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CAMCOG	Cambridge Cognitive Examination
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CHD	Coronary heart disease
CDR	Clinical dementia rating
CT	Computerized tomography
CVD	Cerebrovascular disease
DBP	Diastolic blood pressure
DM	Diabetes mellitus
DSM III	Diagnostic and Statistical Manual of Mental Disorders, 3th edition
ECG	Electrocardiography
EPESE	Established Populations for Epidemiological Studies of the Elderly Study
FTD	Frontotemporal dementia
HDL	High-density lipoprotein
HIS	Hachinski ischemic score
IADL	Interactive active daily living
ICD-10	International Statistical Classification of Diseases and Related Health Problems
ICH	Intracerebral hemorrhage
IHD	Ischemic heart disease

LDL Low-density lipoprotein

MID Multi infarct dementia

MMSE Mini Mental Status Examination

MRI Magnetic Resonance Imaging

NFT Neurofibrillary tangles

NINCDS-ADRDA National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association

NINDS-AIREN National Institute of Neurological Disorders and Stroke – Association Internationale pour la Recherche et l'Enseignement en Neurosciences

OR Odds ratio

PCR Polymerase chain reaction

PSD Poststroke dementia

SAM Helsinki Stroke Aging Memory Study

SBP Systolic blood pressure

SPMSQ Short Portable Mental Status Questionnaire

TIA Transient ischemic attack

TGC Triglyceride

VaD Vascular dementia

VCI Vascular cognitive impairment

VCD Vascular cognitive disorder

VPB Ventricular premature beat

WHO World Health Organization

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following articles, referred to in the text by their Roman numerals I-IV in the text.

I **Sari Rastas,** Kimmo Mattila, Auli Verkkoniemi, Leena Niinistö, Kati Juva, Raimo Sulkava, Esko Länsimies. Association of apolipoprotein E genotypes, blood pressure, blood lipids and ECG abnormalities in general population aged 85+. BMC Geriatr 2004;29:4:1.

II **Sari Rastas**, Tuula Pirttilä, Petteri Viramo, Auli Verkkoniemi, Pirjo Halonen, Kati Juva, Leena Niinistö, Kimmo Mattila, Esko Länsimies, Raimo Sulkava. Association between Blood Pressure and Survival over Nine Years in a General Population Aged 85 Years and Over. J Am Geriatr Soc 2006;54:912-918.

II b **Sari Rastas,** Tuula Pirttilä, Petteri Viramo, Auli Verkkoniemi, Pirjo Halonen, Kati Juva, Leena Niinistö, Kimmo Mattila, Esko Länsimies, Raimo Sulkava. Response letter to Dr Cheng. J Am Geriatr Soc 2007; 55:137.

III **Sari Rastas,** Auli Verkkoniemi, Tuomo Polvikoski, Kati Juva, Leena Niinistö, Kimmo Mattila, Esko Länsimies, Tuula Pirttilä, and Raimo Sulkava. Atrial Fibrillation, Stroke and Cognition: A Longitudinal Population Based Study of People Aged 85+. Stroke 2007;38:1454-1460.

IV **Sari Rastas,** Tuula Pirttilä, Kimmo Mattila, Auli Verkkoniemi, Kati Juva, Leena Niinistö, Esko Länsimies, Raimo Sulkava. Vascular risk factors and dementia in the general population aged 85+. Prospective population-based study. Neurobiol Aging 2008 Mar 29.

CONTENTS

1. INTRODUCTION

The number of old people is increasing exponentially in all western countries adding an enourmous burden of stroke and dementia with their both social and economical costs and not least the individual suffering (Jorm et al., 1987; Rocca et al., 1990; Fratiglioni et al., 1991; Fratiglioni et al., 2000; Lobo et al., 2000; Hollander et al., 2003; Olindo et al., 2003). At the global level, the most rapidly growing age group is that aged 80 and over. This rapidly progressing and worldwide phenomenon has been referred to as the "silver tsunami".

Alzheimer's disease is the most common form of dementia in the older people and it is clearly associated with age. With increasing age, the risk of Alzheimer's disease increases exponentially, being 2.8 per 1000 person-years in the age group 65-69 years up to 56.1 per 1000 person-years in those older than 90-years of age (Kukull et al., 2002). In 95-year olds the prevalence of dementia is as high as 62% (Hofman et al., 1991; Jorm et al., 1994) and in people aged 100 years or over 88% (Blansjaar et al., 2000). Also the incidence of vascular risk factors such as hypertension, diabetes mellitus, and atrial fibrillation increases steeply with increasing age. For example with hypertension, the life time risk is as high as 90%.

The association between vascular risk factors, stroke and dementia is complex. Vascular risk factors are associated with both stroke and dementia and aging itself is a risk for more vascular changes in the brain. Stroke increases steeply the risk of dementia and it can precipitate the onset not only of vascular dementia but also Alzheimer's disease (Tatemichi et al., 1990; Loeb et al., 1992; Tatemichi et al., 1994ab; Hènon et al., 1996; Kalmijm et al., 1996; Snowdon et al., 1997; Honig et al., 2003) and often these two forms of dementias coexist (Tatemichi et al., 1990; Tatemichi et al., 1992; Bornstein et al., 1996; Pohjasvaara et al., 1998; Barba et al., 2000; Desmond et al., 2000; Zhu et al., 2000; Kalaria, 2003; Ivan et al., 2004; Luchsinger et al., 2005).

In the very old, the vascular risk factors for stroke may not be identical to those that have been identified in the middle aged and the association between vascular risk factors with morbidity and mortality is still far from clear.

These studies shed new light on vascular risk factors for stroke and dementia. However, because there is still no cure available for dementia or stroke, their prevention is the most important way to reduce the burden of these diseases.

2. REVIEW OF THE LITERATURE

2.1. Life expectancy and mortality in the very old

2.1.1. Life expectancy

People aged 85 years and over are the fastest growing segment of western populations. In Finland almost half of the men and 70% of women can expect to live to the age of 80 years. Women tend to live longer and their life expectancy is 82.8 years compared to 75.6 years for men (Tilastokeskus väestöennuste, 2007). Mean life expectancy is expected to increase in Finland until the year 2040 in men up to 82.1 years and in women up to 86.3 years. The number of people aged 65 years and over was 15.4% of the total population in the year of 2006 and by 2040 it is expected to increase to 27%. People over 85 years accounted for 1.8% of the total population in 2007 but by the year 2040 that number is estimated to be as high as 6.1% (Tilastokeskus, väestöennuste, 2007).

Not only life expectancy, but also the health of the older people is improving (Freedman et al., 1998; Schoeni et al., 2001). Increase in the life expectancy can be traced to the decrease of ischemic heart diseases (0.6 years) and decreased mortality to lung diseases (0.2-0.3 years) (Valkonen et al., 2007). Several measures of disability and limitations have indicated the functional capacity of the elderly has improved during the last decade, also in Finland (Freedman et al., 2002; Sulander et al., 2007). A person with no functional limitations at the age of 70 years has a life expectancy of 14.3 years and even an idividual with a limitation in at least one activity of daily living still has a life expectancy of 11.6 years (Lubitz et al., 2003).

2.1.2. Factors associated with mortality

The most powerful risk factor for death is age, mainly due to the increasing prevalence with age of vascular and dementing diseases (Agüero-Torres et al., 1998; Lewington et al., 2007). In people aged 85 years and over cardiovascular mortality is 32% (de Ruijter et al., 2009). In Finland more than half of all strokes occur in individuals 75 years or older (Lehtonen et al., 2004) as well as almost half of all myocardial infarctions (Salomaa et al., 2006). In 2006 among Finnish men aged 65 years or over, the five most common causes for death were coronary heart disease (28.8%), cerebrovascular diseases (8.9%), dementia (Alzheimer's disease) (7.9%), lung cancer (6.6%) and prostate cancer (4.5%). In women aged 65 years or over, the corresponding diseases were coronary heart disease (26.8%), dementia (Alzheimer's disease) (15.3%), cerebrovascular diseases (12.4%), other heart diseases (not coronary heart disease) (4.5%), and diseases of the digestive organs (3.5%) (Tilastokeskus, väestöennuste, 2007).

Since dementia (Alzheimer's disease and vascular dementia) is a major health problem in the older people, it contributes strongly to the mortality, in fact it is the leading cause of death in that age-group (van Dijk et al., 1991; Mölsä et al., 1995; Börjesson-Hanson et al., 2004). In one study, examining subjects aged 85 years old, dementia was present in 31% of all deaths in men and 50% of all deaths in women during seven year follow up (Aevarsson et al., 1998). In a five year follow-up of subjects aged 95 years old, dementia was present in 44% of all deaths in women and 30% in men. In 95 year-olds, only 4% in subjects with dementia will reach the age of 100 years compared with 27% of the subjects without dementia (Börjesson-Hanson et al., 2004).

2.2. Dementia in the very old

2.2.1. Criteria for dementia

Dementia is a syndrome that is caused by many different diseases. Dementia is defined as a deterioration from the previous level of memory and higher intellectual function, which impairs the ability of affected persons to function independently. Delirium and other non-organic mental disorders must be excluded. Dementia may be progressive,

static, or remitting (American Psychiatric Association 1994). The dementia syndrome is divided into three categories: mild, moderate, and severe. There are several criteria to define dementia syndrome; the most widely used criteria are Diagnostic and Statistical Manual of Mental Disorders, 3th edition, revised, (DSM III-R) (American Psychiatric Association, 1987), Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (American Psychiatric Association, 1994), and International Statistical Classification of Diseases and Related Health Problems (ICD-10) (WHO, 1992).

ICD-10	Requires memory decline and a decline in other cognitive abilities sufficient to impair personal activities of daily living. The awareness of the environment has to be preserved. A decline in emotional control or motivation or a change in social behaviour has to be established. The criterion should have been present for at least six months (WHO 1992).
DSMIII-R	A) impairment in short-and long term memory B) impairment in abstract thinking or judgement or impairment of higher cortical function or personality changes an C) evidence that the cognitive disturbance resulting from criteria (A) and (B) significantly interferes with work, usual social activities or relationships with others. Symptoms do not occur exclusively during the course of delirium (D) and there is either (E1) evidence of a specific organic factor judged to be etiologically related to the disturbance, or (E2) in the absence of such evidence, an etiological factor can be presumed if the disturbance cannot be accounted for by any non-organic mental disorder (American Psychiatric Association 1987).
DSM-IV	Development of multiple cognitive deficits including memory impairment and at least one of the following cognitive disturbances: aphasia, apraxia, agnosia, or a disturbance in executive functioning. The cognitive deficits must be sufficiently severe to cause significant impairment in social or occupational function and must represent a significant decline from a previously higher level of functioning (American Psychiatric Association 1994).

Table 1. The most widely used criteria for dementia.

2.2.2. Prevalence and incidence of dementia

The lifetime risk of dementia is 33% for women and 20% for men (Ott et al., 1995). The incidence and prevalence of the dementia syndrome increases almost exponentially with increasing age. About 1% of people 65 to 69 years of age have dementia rising to about 60% of people aged ≥95 years (Jorm et al., 1987; Rocca et al., 1990; Zhang et al., 1990; Fratiglioni et al., 1991; Fratiglioni et al., 1999). Among people aged≥ 85 years the prevalence of dementia is 42.9% in men and 50.9% in women (Fitzpatrick et al., 2004). However, the prevalence of dementia varies widely in different studies since there are different definitions for dementia. In the Helsinki Stroke Aging Memory (SAM) study, the frequency of dementia varied according to different criteria in subjects aged 75-85 years from 10.3% according to ICD-10 criteria to 18.4%, according to DSM-IV criteria, 26.2% according to DSM-III –R, and 25.5% according to DSM-III criteria (Pohjasvaara et al., 1997). In a study from Gothenburg, the prevalence among people aged 85 years and over was 29.8% according to DSM-III-R (Skoog et al., 1993). In the Helsinki Aging Study, the prevalence of dementia among the 85 year olds was 26.7% according to DSM-III-R (Juva et al., 1993). In very old people aged 95 years, the prevalence of dementia was as high as 51.5% according to DSM III-R (Börjesson-Hanson, 2004) and in people aged 100 years and over as many as 88% suffer from dementia (Blansjaar et al., 2000).

The incidence of dementia has been estimated to range from 5 to 10 cases per 1000 person-years at 70 years and older (Fratiglioni et al., 1999). In subjects aged over 80 years the incidence rates vary from 20 to 99 cases per 1000 person-years (Hagnell et al., 1991; Hebert et al., 1995; Aevarsson and Skoog, 1996; Fratiglioni et al., 1999; Fitzpatrick et al., 2004). A meta-analysis of 23 studies revealed that the incidence of dementia in subjects aged 90-94 years was 179 cases per 1000 person-years (Jorm et al., 1998). However, there is evidence that cognitive functions may be improving in the elderly. A recent American study suggested that significant cognitive impairment in individuals aged 70 years or older was less prevalent in the year 2002 than it had been in year 1993 (Langa et al., 2008).

2.2.3. Main causes of dementia in the very old

The most common causes for dementia in the older people (aged 65 years or older) are Alzheimer's disease (AD), vascular dementia (VaD), dementia with Lewy bodies and dementia associated with Parkinson's disease. The different forms of dementia may also exist together.

2.2.3.1. Alzheimer's disease

2.2.3.1.1. Clinical features of Alzheimer's disease

AD is a progressive, age-related neurodegenerative disorder resulting in major disability and loss of independence that is devastating for the patient, care-givers and family. There is a typical clinical picture characterized by memory problems, executive dysfunction, aphasia, apraxia, agnosia, and visuospatial difficulties. The preclinical pathological stages of AD disease extend over years or even decades before the onset of disease (Troncoso et al., 1998). Sporadic AD manifesting after age 65 is the most common form of AD. It is multifactorial with an unknown ethiology (Breteler, 2001). AD may even be a complex mixture of different disease pathologies rather than one entity (Skoog et al., 1999).

The most widely used clinical criteria for diagnosing AD are those devised by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA), which divides AD into three categories: mild, moderate, and severe (McKhann et al., 1984). The criteria for probable AD are mainly based on the exclusion of other possible causes for progressive cognitive decline in a subject suffering from dementia.

2.2.3.1.2. Prevalence and incidence of Alzheimer's disease

AD is the leading cause of cognitive decline accounting for 50-70% of all dementias (Breteler et al., 1992; Breteler, 2001) and it is estimated to have affected at least 26.6

(range 11.4-59.4) million people worldwide in the year 2006 (Brookmeyer et al., 2000). The prevalence of AD increases strongly with age from 1% in subjects aged 60-64 to 13%- 47% in people aged 85 years or over (Fratiglioni et al., 1991, Bachman et al., 1992; Skoog et al., 1993; Ott et al., 1995) and increasing to as high as 50% in 95-year-olds (Börjesson-Hanson et al., 2004).

The incidence of AD clearly increases with age but may decline in the extremely old (Jorm et al., 1998; Miech et al., 2002). It seems to almost double every five years up to age 90 years and is higher in women after age 85 (Ruitenberg et al., 2001, Miech et al., 2002). In individuals aged 85-89 years, the incidence of AD has been estimated to range from 38.03 to 44.90 cases per 1000 person-years (Launer et al., 1999; Miech et al., 2002) and in people older than 90 years it is 56.1 cases per 1000 person-years (Kukull et al., 2002). Due to the aging of the population, the number of sufferers is predicted to grow by fourfold, to 106.8 million by the year 2050 (Brookmeyer, 2000).

2.2.3.1.3. Risk factors for Alzheimer's disease

Several risk factors for AD have been identified, although the exact mechanisms by which these factors contribute to the development of the disease remain obscure. Advancing age is the predominant risk factor for AD and beyond the age of 65, the risk of AD increases exponentially (Fratiglioni et al., 2000; Lobo et al., 2000). The role of gender is not entirely clear, but current studies suggest that women may be more susceptible than men (Launer et al., 1999; Fratiglioni et al., 2000; Lobo et al., 2000; Gorelick, 2004).

A positive family history seems to be a consistent risk factor for AD and about 30% of AD cases have a positive family history though the risk seems to decrease with increasing age (Silverman et al., 2005; Jayadev et al., 2008). The genetic determinants of AD are complex and seem to play a greater role in younger ages (McMurtray et al., 2006). The most important genetic susceptibility factor in late-onset AD is the polymorphism of apolipoprotein E where the possession of the ε4 allele increases the risk of dementia from 2 to 3 fold (Lindsay et al., 2002; Hsiung et al., 2004; Heun et al., 2006; Mayeux, 2006; Qiu et al., 2006a; Sando et al., 2008a). The risk for AD increases

also with Down's syndrome. Individuals with this syndrome carry an extra copy of chromosome 21, where the gene for amyloid precursor protein is located (Mann and Esiri, 1989).

Low education has been consistently shown to be associated with increased risk of dementia and AD (Friedland, 1993; Katzman, 1993; Stern et al., 1994; Butler et al., 1996; Sando et al., 2008b). Other risk factors for AD include depression and psychological stress (Ownby et al., 2006; Luchsinger et al., 2008), head trauma (Mortimer et al., 1991; Rasmusson et al., 1995; Gottlieb, 2000; Lye and Shores, 2000; Fleminger et al., 2003; Luukinen et al., 2005) and viruses (Pyles, 2001; Letenneur et al., 2008). In addition, some life-style factors such as obesity (Gorospe and Dave, 2007; Beydoun et al., 2008; Luchsinger and Gustafson, 2009), heavy drinking (Huang et al., 2002; Lindsay et al., 2002; Ruitenberg et al., 2002; Anttila et al., 2004), physical inactivity, (Scarmeas et al., 2001; Yaffe et al., 2001; Lindsay et al., 2002; Podewils et al., 2005; Rovio et al., 2005), mental inactivity (Scarmeas et al., 2001; Wilson et al., 2002) poor social networks or loneliness (Seeman et al., 2001; Scarmeas et al., 2001; Rovio et al., 2005) have been shown to associate with AD.

Several common vascular risk factors such as hypertension (Skoog et al., 1996; Haan et al., 1999; Harrington et al., 2000; Elias et al., 2003; Piguet et al., 2003; Skoog, 2003; Waldstein et al., 2005; Reitz et al., 2007), diabetes mellitus (DM), (Elias et al., 1997; Fontbonne et al., 2001; Knopman et al., 2001; Peila et al., 2002; Arvantakis et al., 2004; Hassing et al., 2004), hyperlipidemia (Notkola et al., 1998; Michikawa, 2003; Reitz et al., 2004;; Li et al., 2005; Hayden et al., 2006), hyperhomocystinemia, smoking, and transient ischemic attack (TIA) (Launer et al., 1999; De la Torre, 2002; Launer, 2002; Seshadri et al., 2002; Iadecola and Gorelick, 2003; Luchsinger et al., 2005; Aggarwal et al., 2006) have been shown to affect the risk of AD. High blood pressure (BP) and hyperlipidemia particularly in midlife have been shown to increase the risk of AD in late life (Skoog et al., 1996; Launer et al., 2000; Kivipelto et al., 2002; Kivipelto et al., 2005; Whitmer et al., 2005). However, very few studies have evaluated the influence of these risk factors for AD in the very old people (85 years or older).

2.2.3.2. Vascular dementia

2.2.3.2.1. Definition of vascular dementia

VaD is a heterogeneous disorder, caused by focal, multifocal or diffuse vascular and/or ischemic lesions involving various, often functionally important, brain areas and neuronal networks with deafferentation of frontal and limbic cortical structures and interruption of basal ganglia-cortical, corticocortical and ascending pathways by lesions in basal ganglia, thalamus, white matter and subfrontal areas (Jellinger, 2007). The clinical features include lateralized sensomotor changes and an abrupt onset of cognitive impairment and aphasia (Erkinjuntti, 1987) or cortical neuropsychological syndromes (Mahler et al., 1991). Pure motor hemiparesis, bulbar signs or dysarthria, depression and emotional lability may also exist (Ishii et al., 1986; Babikian and Ropper, 1987; Mahler et al., 1991).

VaD has been defined as a consequences of strokes, large or small (Fisher, 1968), but also named as multi-infarct dementia (MID) (Hachinski et al., 1974), poststroke dementia (PSD) (Leys et al., 2005; Reitz et al., 2008), vascular cognitive impairment (VCI) (O'Brien et al., 2003; Bowler, 2007; Rockwood et al., 2007) or vascular cognitive disorder (VCD) (Román et al., 2004). VCI refers to all ethiologies of cerebrovascular disease including vascular risks which can result in brain damage leading to cognitive impairment and it is currently considered as the most up-to-date version of the terminology (O'Brien et al., 2003). A recent study suggested that subcortical vascular disease may be the most common form of VCI (Erkinjuntti, 2003). However, the clinical criteria for VaD still remain rather incomplete and no well validated criteria have been established to date (Chui et al., 2000; Román 2003; Lopez et al., 2005; Bacchetta et al., 2007; Murray et al., 2007). The most widely used criteria up to early 90's for VaD were Hachinski Ischemic Score (HIS) (Hachinski et al., 1975), DSM III (APA, 1980) or DSM III-R (APA, 1987). The criteria devised by the National Institute of Neurological Disorders and Stroke –Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINCDS-AIREN) criteria have been used in many studies (Román et al., 1993).

2.2.3.2.2. Prevalence and incidence of vascular dementia

VaD is the second most important cause of dementia in the older people after AD (Rocca et al., 1991; Hébert and Brayne 1995; von Strauss et al., 1999; Lobo et al., 2000; Dubois and Hébert, 2001; Román, 2003) accounting for 15-20% of all dementia cases worldwide (Lobo et al., 2000; Dubois and Hébert, 2001). In the oldest age group, the proportion of VaD may be lower than in younger people (von Strauss et al., 1999; Börjesson-Hanson et al., 2004) but the combination of AD and VaD seems to be particularly frequent in the very old (Kalaria, 2000). Since there is no clear consensus about the diagnostic criteria of VaD, both prevalence and incidence rates are highly variable. According to different studies, the prevalence of VaD ranges from 5.4% up to 39% (Kase 1991; Fratiglioni et al., 1997; Lobo et al., 2000; Rockwood et al., 2000; Rahkonen et al., 2003). Neuropathologic studies show that prevalence of VaD also varies extensively from 0.03% to 85.2% (Seno et al., 1999; Akatsu et al., 2002; Riekse et al., 2004; Jellinger, 2007) probably due to differences in the research cohorts and neuropathological criteria.

The incidence rates for VaD are highly dependent on age. The risk of VaD is higher in men than women in all age groups (Ruitenberg et al., 2001). The incidence of VaD in the age group <70 years is 0.7 or 3.9 to 6-8 cases per 1000 person-years and in the age group 80 years and over it rises up to 50 cases per 1000 person-years (Fratiglioni et al., 2000; Kuller et al., 2005; Bowler, 2007). Several studies have found the incidence in older populations vary between 1.5 and 3.3 per 1000 person-years in older populations (Hébert et al., 2000; Ruitenberg et al., 2001; Di Carlo et al., 2002).

2.2.3.2.3. Risk factors for vascular dementia

There are several established risk factors for VaD, most of them are the same as the risk factors as for stroke (Gorelick et al., 1993). Age, male sex, and low education have been documented as risk factors for VaD (Rocca et al., 1991; Gorelick and Roman, 1993; Tatemichi et al., 1994a; Bonaiuto et al., 1995). There are many vascular risk factors

such as hypertension (Ladurner et al., 1982; Yoshitake et al., 1995; Hèbert et al., 2000), smoking (Gorelick et al., 1993), DM (Desmond et al., 1993; Landin et al., 1993; Tatemichi et al., 1993; Ott et al., 1996; Raffaitin et al., 2009), myocardial infarction (Gorelick et al., 1993), atherosclerosis (Kannel et al., 1983; van Oijen et al., 2007), hyperlipidemia (Desmond et al., 1993; Stella et al., 2007), metabolic syndrome (Raffaitin et al., 2009), heart disease, atrial fibrillation (AF) (Lindsay et al., 1997; Ott et al., 1997; Meyer et al., 1998; Hèbert et al., 2000; Román, 2005), hyperhomocysteinemia (Hassan et al., 2004; Román, 2005), apolipoprotein E (Couderc et al., 1993; Frisoni et al., 1994; Baum et al., 2006, Davidson et al., 2006). Genetic risk factors such as cerebral autosomal dominant arteriopathy with subcortical infarct and leucoencephalopathy (CADASIL) are well established risk factors for VaD (Bowler and Hachinski, 1994; Bousser and Tournier-Lasserve 1994; Sourander and Walinder, 1997). In addition also stroke associated factors such as the volume or strategic location of the infarction, the number of infarcts, and the degree of cerebral atrophy have been documented as risk factors for VaD (Tomlison et al., 1970; Loeb et al., 1988; Gorelick et al., 1992; Liu et al., 1992; Desmond et al., 1993; Tatemichi et al., 1993).

2.3. Brain pathologies that contribute to cognitive decline

2.3.1. Neuropathological features of primary degenerative dementias

The characteristic pathological features of AD are an accumulation of amyloid plaques (Haroutunian et al., 1998; Morris and Price, 2001) and neurofibrillary tangles (NFT) in the entorhinal cortex, hippocampus, and cerebral neocortex (Braak and Braak, 1995). However, amyloid plaques and NFTs have also often been found from the brains of cognitively intact subjects i.e. normal aging (Haroutunian et al., 1998; Davis et al., 1999; Schmitt et al., 2000; Knopman et al., 2003; Bennet, 2006). Some researchers have suggested that these changes represent pathological ageing (Crystal et al., 1993) or presymptomatic AD (Morris et al., 1996). An other neurodegenerative process that may contribute to cognitive decline is the accumulation of alpha-synuclein in Lewy bodies. These changes develop neocortically and subcortically, particularly in substantia nigra,

locus ceruleus, substantia innominata, and dorsal vagus nucleus. Some restricted subcortical changes are found in Parkinson's disease (Gibb et al., 1990; Hansen and Galasko, 1992; Perry et al., 1990) whereas a more widespread neocortical pathology is characteristic for Lewy body dementia (McKeith, 1996; Braak et al., 2006). However, the contribution of alpha-synuclein to cognitive decline remains unclear since the precence of Lewy bodies and alpha-nuclein inclusions are common in asymptomatic elderly individuals (Bergeron and Pöllänen, 1989; Knopman, 2003).

2.3.2. Neuropathological features of vascular dementia

Vascular pathology contributes also to cognitive decline. Large vessel disease, previously called multi-infarct dementia, is attributed to atherothrombotic strokes, cardiac embolic strokes, and cortical distal field infarcts (Erkinjuntti, 1999). Small vessel disease refers to lacunes or microinfarcts involving deep local or diffuse white matter and subcortical structures such as thalamus, basal ganglia, internal capsule and brain stem (Bouras et al., 2006). The pathogenesis for small vessel diseases is mainly due to hyalinosis, amyloidosis, vasculitis, or thrombosis (Jellinger, 2007; Liem et al., 2007). The number, volume and location of vascular lesions have been associated with the severity of the cognitive decline (Tomlinson et al., 1970; del Ser et al., 1990; Fein et al., 2000; Kövari et al., 2004; Gold et al., 2005; Tomimoto et al., 2007). However, there are still no well standardized protocols for the neuropathological assessment of vascular pathology. A recent study revealed the significant heterogeneity for assessing lesions with possible or even definite vascular origin and surprisingly, also in the classification of what lesions are considered to represent an expression of vascular involvement (Pantoni, 2006).

2.3.3. Co-existence of brain pathologies

Multiple co-existent brain pathologies contribute to cognitive decline and increase the odds of dementia in the very old. The co-morbidity of AD and cerebrovascular disease is well known (Sadowski et al., 2004; Schneider et al., 2004; Jellinger 2007) and at least 30% of AD subjects display evidence of cerebral infarction (Olichney et al., 1997). The prevalence of vascular pathology increases with age and many studies have suggested that at least half of elderly subjects have both AD and vascular brain lesions (Xuereb et al., 2000; Fernando et al., 2004; Schneider et al., 2007). Vascular factors may increase the severity of dementia by affecting the same regions as those damaged by AD or by adding deficits in other regions (Snowdon et al., 1997; Skoog 1998; Schneider et al., 2004). Subcortical infarcts increase the odds of dementia by almost four-fold through their interaction with AD pathology (Schneider et al., 2004). Some studies suggest that neurovascular dysfunction could have a major role in the pathogenesis and progression of AD (Zlokovic, 2005; Mielke et al., 2007).

The majority of older people have brain pathology (Schneider et al., 2007) but the impact of distinct pathologies on cognitive functioning becomes less serious with age. Many studies have shown that the plaque and tangle load has a poor correlation with the severity of dementia in the very old (Giannakopoulos et al., 1996; Mungas et al., 2001; Prohovnik et al., 2006). In one study, almost 50% of demented subjects aged 80 or older did not meet pathological criteria for AD or Lewy body dementia (Crystal et al., 2000).

2.4 Stroke

2.4.1. Definition of stroke

There are three pathological types of stroke: ischaemic stroke (about 80%), primary intracerebral haemorrhage (about 15%), and subarachnoid haemorrhage (about 5%) (Warlow et al, 2003). Ischemic stroke is caused by the interruption of the blood supply to a part of the brain, usually because a blood vessel has burst or is blocked by a clot. This cuts off the supply of oxygen and nutrients, causing damage to brain tissue. The

most common symptom of a stroke is sudden weakness or numbness of the face, arm and/or leg, most often on one side of the body. Other symptoms include: dysphasia, confusion, difficulties seeing with one or both eyes, difficulties in walking, dizziness, loss of balance or coordination, severe headache with no known cause, fainting or unconsciousness. By definition, the symptoms should last for more than 24 hours (WHO, 2008).

The most important ethiologies of ischemic stroke include large artery atherosclerosis (macroangiopathy), cardioembolism (about 20%), and cerebral small-vessel disease (microangiopathy). Less common causes of stroke include cervical artery dissection, cerebral vasculitis, coagulopathies, hematologic disorders, and others (Grau et al., 2001; Warlow et al., 2003).

2.4.2. Prevalence and incidence of ischemic stroke

The worldwide burden of stroke is enormous both socially and economically. The prevalence of stroke increases with male sex and age even at≥85 years (Zhu et al., 1998; Hollander et al., 2003; Olindo et al., 2003; Rothwell et al., 2005; Goldstein et al., 2006). Recently it was predicted that the number of stroke events in Europe will increase from 1.1 million per year in 2000 to more than 1.5 million per year in 2025, based only on demographic changes (Truelsen et al., 2006). In subjects aged 85 to 88 years old, the prevalence of stroke has been reported to be 18.8% (Liebetrau et al., 2003). Stroke is more prevalent in men than in women (Brown et al., 1996; Lewsey et al., 2009), but in those aged 85 years and over, women have a greater age-specific incidence than men (Sacco et al., 1997; Glader et al., 2003; Rothwell et al., 2005; Petrea et al., 2009). The lifetime risk of stroke decreases in the very old because the remaining life expectancy decreases more rapidly than the risk of stroke increases (Seshadri et al., 2006).

There is a remarkable variation in stroke incidence in different populations (He et al., 1995; Stegmayr et al., 1997). In some populations, the incidence of stroke rates decreased up to the 1970s, but since then they have remained essentially unchanged (Brown et al., 1996; Numminen et al., 1996; Moriwaka et al., 2000; Terént, 2003). The

incidence of stroke increases steeply with age and 75% of strokes occur in individuals over than 65 years (Rodgers et al., 2004; Goldstein et al., 2006; Hallström et al., 2008). In subjects between 85 and 88 years, the incidence of firstever stroke has been reported to be 57 per 1000 person-years (Liebetrau et al., 2003). In the Rotterdam Study, the incidence of stroke in people aged 85 years to 89 years was 22 per 1000 person-years (Hollander et al., 2003). In subjects aged 85 years and over the incidence rate of firstever stroke has been reported to be 18.2-32 per 1000 person-years (Thrift et al., 2001; Iemolo et al., 2002; Olindo et al, 2003).

In Finland, the stroke incidence has been one of the highest in the world (Tuomilehto et al., 1996). However, declining trends in the incidence have been observed since the beginning of the 1980s also in the oldest age group in patients aged ≥85 years old (Thorvaldsen et al., 1995; Lehtonen et al., 2004; Sivenius et al., 2004; Pajunen et al., 2005). However, silent strokes are common in the elderly and in one study of people aged ≥65 years during the five years of follow up 17.7% developed an incident infarct in follow-up MRI though over the same period, only 2.7% of the participants suffered clinical stroke (Longstreth et al., 2002).

2.4.3. Risk factors for stroke

There are several well established risk factors for stroke and it is common that individuals exhibit numerous risk factors for stroke in the same time. However, it is not clear whether these risk factors are important also in the very old (Hollander et al., 2003). The effect of age on the risk of brain infarction is well established (Salonen et al., 1982; Lin et al., 1984; Iso et al., 1989; Pohjasvaara et al., 2000; Hajat et al., 2001; Desmond et al., 2002). The risk of stroke doubles in each successive decade after the age of 55 years in both men and women (Wolf et al., 1992; Brown et al., 1996). Women tend to have their first-ever stroke on an average of five years later than men (Petrea et al., 2009). Low socioeconomic status and depression have been shown to associate with the risk of stroke (Jakovljevic et al., 2001; Avendano et al., 2006; Liebetrau et al., 2008; McFadden et al., 2009). Both paternal and maternal histories of stroke have been associated with an increased stroke risk (Welin et al., 1987; Kiely et al., 1993;

Tentschert et al., 2003). A few rare genetic conditions such as CADASIL are associated with an increased risk of stroke (Kalimo et al., 1999; Román et al., 2002; O'Brien et al., 2003; Peters et al., 2004).

Hypertension is the most important modifiable vascular risk factor not only for ischemic stroke but also for hemorrhagic stroke (Kaarisalo et al., 2000; Grau et al., 2001; Ohira et al., 2006; Ikeda et al., 2009). The incidence of stroke increases with both high systolic blood pressure (SBP) and diastolic blood pressure (DBP) (MacMahon et al., 1991). Hypertension carries a risk for stroke even when treated (Almgren et al., 2005; Li et al., 2005; Harmsen et al., 2006). It also increases the risk of mortality from stroke (Ikeda et al., 2009). However, in older people, it has been suggested that the impact of hypertension to stroke may decrease with age (Whisnant et al., 2002).

AF is an important and treatable risk factor for stroke and its impact persists up to the ninth decade of life (Wolf et al., 1991a; Sandercock et al., 1992; Jørgensen et al., 1995; Lin et al., 1996; Andersen et al., 2009) although in one study, the stroke risk diminished in later life (Harmsen et al., 2006). DM is a clear risk factor for stroke itself and also via comorbidity of atherosclerosis and other vascular risk factors such as dyslipidemia, obesity, and hypertension (Sacco et al., 1997; Andersen et al., 2009). The association of lipids (Iso et al., 1989; Benfante et al., 1994; Hachinski et al., 1996; Imamura et al., 2009) and obesity (Simons et al., 1998; Rodgers et al., 2004) with stroke remains uncertain in the very old. However, the metabolic syndrome has been shown to associate with an increased risk of stroke in older people (Milionis et al., 2005a; Milionis et al., 2005b; Maruyama et al., 2009). Previous stroke has been shown to increase the risk of recurrent stroke in several studies (Hajat et al., 2001; Andersen et al., 2009). Subjects with an asymptomatic carotid artery stenosis in the range between 50% and 99% have an annual stroke risk 1%-3.4% (Bogousslavsky et al., 1986; Chambers and Norris, 1986; Meissner et al., 1987; Mackey et al., 1997). Homocysteine has been shown to be a risk factor for stroke also in elderly (Welch and Loscalzo, 1998; Bostom et al., 1999; Homocysteine Studies Collaboration, 2002; Tanne et al., 2003; Casas et al., 2005). There is a J-shaped curve between alcohol consumption and ischemic stroke risk and several studies claim that light or moderate alcohol consumption is associated with lower risk of stroke (Gorelick et al., 1989; Hillbom et

al., 1999; Klatsky et al., 2001; Djousse et al., 2002; Iso et al., 2004a). Smoking approximately doubles the risk of stroke (Manolio et al., 1996; Rodriguez et al., 2002; Mostaza et al., 2009). Recently, it was reported that depression is associated with an increased risk of firstever stroke in subjects aged 85 years old (Liebetrau et al., 2008).

2.4.4. Prevalence and incidence of cognitive decline after stroke

Until the 1960s, most cases of dementia were attributed to atherosclerosis. Stroke increases the risk of dementia from 4 to 12 times (Tatemichi et al., 1992; Cencori et al, 1996; Inzitari et al., 1998; Pohjasvaara et al., 1998; Barba et al., 2000; Knopman et al., 2009a) and even asymptomatic strokes increase the risk of dementia (Vermeer et al., 2003; Schneider et al., 2004; Gamaldo et al., 2006).

The estimates of the prevalence of cognitive deficits after stroke vary extensively from 8.3% to 82% (Tatemichi et al., 1990; Loeb et al., 1992; Bornstein et al., 1996; Kokmen et al. 1996; Barba et al., 2000; Zhu et al., 2000; Hènon et al., 2001; Rasquin et al., 2004; Leys et al., 2005; Reitz et al., 2008). These differences are explained by the criteria of cognitive impairment, time interval from stroke onset, and the selection of patients. The majority of subjects who become demented after stroke do so in the first year (Pohjasvaara et al., 1998; Desmond et al., 2000; Gamaldo et al., 2006).

The incidence rate of PSD also varies extensively. In one community based study with a follow-up time over 25 years, the cumulative incidence of dementia after stroke was 7% after one year, 10% after three, 15% after five, 23% after ten, and 48% after 25 years (Kokmen et al., 1996). In hospital based studies, the incidence of PSD was 9% (Ballard et al., 2003) after one year, 21.5% to 28.5% after three years (Hénon et al., 2001; Altieri et al., 2004), and 32% after five years (Tatemichi et al., 1994a; Bornstein et al., 1996). Very old people are especially prone to suffer dementia after stroke. In 85-years olds, the prevalence of dementia is 57.0% if there has been a previous stroke compared to 23.5% of those without (Liebetrau et al., 2003). However, recovery from PSD to nondementia may also be also possible (Snaphaan and de Leeuw, 2007). Over 70% of strokes are first events (American Heart Association 2003) and thus the primary

prevention of strokes is the best way to prevent PSD (Gorelick 1995; Sacco et al., 1997).

2.4.5. Stroke and Alzheimer's disease

AD and VaD have traditionally been considered as separate diseases. However, recent studies have revealed extensive overlap in symptomatology, risk factors, and pathophysiology between these two diseases (Agüero-Torres and Windblad, 2000; Groves et al., 2000; Kalaria, 2003). Stroke can precipitate the onset of AD (Hènon et al., 1996; Kalmijm et al., 1996; Snowdon et al., 1997; Honig et al., 2003) and VaD and AD coexist frequently (Tatemichi et al., 1990; Tatemichi et al., 1992; Pohjasvaara et al., 1998; Barba et al., 2000; Desmond et al., 2000; Zhu et al., 2000; Ivan et al., 2004).
In some cases, dementia occurring after stroke has a progressive onset and insidious course which may reflect a degenerative process (Tatemichi et al., 1990; Erkinjuntti and Hachinski, 1993; Pasquier et al., 1995; Hénon et al., 1996; Pasquier and Leys, 1997). It has been estimated that between 9.2-16.0% of the PSD cases may have had pre-existing undiagnosed degenerative dementia (Tatemichi et al., 1992; Hènon et al., 1997; Inzitari et al., 1998; Pohjasvaara et al., 1999; Barba et al., 2000). In the Framingham Study, the majority of stroke subjects (37%) developed either VaD or mixed dementia (AD with VaD) (Ivan et al., 2004). The presence of stroke affects the risk of developing AD even more in those subjects with other cardiovascular risk factors such as hypertension, AF, DM, or heart disease (Ott et al., 1997; Ott et al., 1999; Honig et al., 2005; de Haan et al., 2006). The APOE ε4 allele frequency is increased both in VaD and AD (Frisoni et al., 1994; Kalmijin et al., 1996) and the risk of dementia increases in stroke survivors with the APOE ε4 allele (Margaglione et al., 1998).

2.4.6. Stroke and mortality

In global terms, stroke is one of the most common causes of death. Stroke mortality varies widely between countries from which routine death-certificate data are available (Håheim et al., 1993; Thorvaldsen et al., 1995; Warlow et al., 2003; Lopez et al., 2006).

Stroke mortality declined as much as 60% in the years 1968-1996 after which it reached a plateau (Brown et al., 1996). The decrease in stroke mortality rates most probably results from improved survival rather than from any decline in morbidity. However, by the year of 2020, stroke mortality will be almost doubled, mainly as a result of the increase in the proportion of older people in the population (Warlow et al., 2003).

Despite advances in prevention, acute care, and rehabilitation the prognosis after acute stroke remains poor: 20-30% of patients die within a month and 13% of survivors are discharged to institutional care (Wolf et al., 1992; McGovern et al., 1993). In the Multinational MONItoring of trend and Determinants in Cardiovascular Disease (WHO MONICA) project during the ten years follow-up of all strokes 22% were fatal within 28 days among men and 25% among women (Tuomilehto et al., 1996). In line with this was study which showed increased mortality in women compared to men aged 85 and over (Liebetrau et al., 2003). However, stroke patients over 90 years have 5-8 times higher mortality when compared to patients aged <70 years. The oldest age group has also longer hospitalization, and is less likely to be discharged to their original place of residence (Saposnik et al., 2009). One study reported even 59.8% deaths within 30 days in stroke patients aged 80 years and older (Marini et al., 2004). In subjects aged 85 years and over there is 14-15% excess in stroke mortality in women compared to men (Reeves et al., 2008; Lewsey et al., 2009). More than one year after first stroke, the excess mortality appears to level off the risk for death being approximately twice that of the general population (Dennis et al., 1993; Loor et al., 1999; Hankey et al., 2000).

Several vascular risk factors such as elevation in SBP or DBP, DM, AF, or smoking increase the stroke mortality (Shinton and Beevers, 1989; Kawachi et al., 1993; Tanne et al., 1997; Vernino, et al., 2003; Hu et al., 2005). Other factors that associate with stroke mortality are age, stroke severity, or previous history of stroke/transient ischemic attacs (TIA) (Chambers et al., 1987; Bonita et al., 1988; Hankey et al., 1998; Woo et al., 1992; Vohra et al., 2000; Carter et al., 2007). The dementia syndrome is an independent risk factor for mortality, either preceding the stroke or appearing in the three months after increasing the risk of mortality approximately three-fold (Tatemichi et al., 1994b; Barba et al., 2002).

2.5. Vascular risk factors and their influence on morbidity and mortality in the very old

2.5.1. Apolipoprotein E

2.5.1.1. Definition and prevalence of apolipoprotein E

Apolipoprotein E (apoE) is a polymorphic multifunctional protein which has a major role in normal lipid transportation and cholesterol metabolism (Mahley, 1988). It is polymorphic and exists in three main protein isoforms designated E2, E3 and E4 encoded by three alleles ε2, ε3, 4ε (Davignon et al., 1988; Mahley, 1988). The proportion of different APOE alleles varies in different populations. The genotype ε3/ε3 occurs in about one half to two thirds of people in most populations (Sudlow et al., 2006). The frequency of the ε4 allele is high in the Finnish population (Ehnholm et al., 1986). The presence of an APOE ε4 allele is associated with increased total cholesterol levels (Davignon et al., 1988; Eichner et al., 2002) and it is thus a significant risk factor for coronary heart disease (Song et al., 2004). The presence of ε2 genotype is associated with decreased levels of cholesterol (Eichner et al., 2002).

2.5.1.2. Apolipoprotein E and stroke

The role of the apoE polymorphism on the cerebrovascular disease is still unclear (Sudlow et al., 2006). APOE ε4 allele enhances amyloid deposition in blood vessels and the ε2 allele predisposes to vasculature patological leading to the rupture of amyloid laden vessels. Thus ε4 and ε2 carriers may have increased susceptibility to intracerebral hemorrhages (ICH) (McCarron and Nicoll, 2000). Some studies have shown an association between APOE ε4 allele and stroke (Abboud et al., 2008; Paternoster et al., 2008) while others have not found any association (Basun et al., 1996; Ferrucci et al., 1997; Zhu et al., 2000; MacLeod et al., 2001). In subjects aged $\geq$75 years the incidence of a first stroke did not vary with apoE polymorphism (Basun et al., 1996). However, in another study there was an age-dependent protective effect of APOE ε2 on the risk of

ischemic stroke in the same age group (Ferrucci, et al., 1997). In neuroimaging studies, the association between APOE ε4 allele and stroke has either been marginal (DeCarli et al., 1999) or non exististent (Kuller et al., 1998). In one autopsy study, the present of the APOE ε4 allele has been associated with about a two-fold increase in the odds of suffering cerebral infarctions (Schneider et al., 2005), while in another study no relationship with cerebral infarctions was found (Olichney et al., 2000).

2.5.1.3. Apolipoprotein E and cognition

ApoE has a dual role in the central nervous system. It is involved both in the regenerative response of injured nerves but it is also associated with age-dependent degenerative diseases (Strittmatter et al., 1993). ApoE has also neurotrophic, immunomodulatory, and antioxidant effects after injury in the central nervous system (Laskowitz et al., 1998). On the other hand, there is a strong association between APOE ε4 allele and AD (Corder et al., 1993; Saunders et al., 1993a; Kuusisto et al., 1994; Poirier, 2003; Bennet et al., 2009). APOE ε4 allele seems to promote the formation of senile plaques and NFTs in AD (Nagy et al., 1995; Polvikoski et al., 1995; Ohm et al., 1999; Ghebremedhin et al., 2001; Tiraboschi et al., 2004). Age may decrease the association between APOE ε4 allele and AD (Farrer et al., 1997; Tang et al., 1998; Juva et al., 2000; Miech et al., 2002). The odds ratio between ε3/4 and ε4/4 declined from 4.8 at ages 75 to 79 years to 1.7 at ages 80 to 84 and to 1.0 at age 85+ (Corder et al., 1996). The relationship between APOE ε2 allele and the risk of AD remains controversial. Surprisingly in one study, E2 allele has been found to be a risk factor for early onset AD (van Duijn et al., 1995), but it has also been found to protect from AD (Farrer et al., 1997). Other studies have shown no protective effect of ε2 on AD (Katzman et al., 1997; Frikke-Schmidt et al., 2001) or no significant decreased risk of the disease (Meyer et al., 1998; Slooter et al., 1998; Yip et al., 2002).

The association between APOE ε4 allele and VaD is controversial. Some studies have found an association between APOE ε4 allele and VaD (Shimano et al., 1989; Frisoni et al., 1994) while others have not found any association (Kuusisto et al., 1994; Stengård et al., 1995). In one study, the possession of the APOE ε4 allele in 85-year-old people

was associated with dementia only in those who had also ischaemic white matter lesions (Skoog et al., 1998b). APOE ε4 has been either associated with greater cognitive decline after stroke (Ballard et al., 2003) or no association has been found (Rowan et al., 2005). In the Rotterdam Study, atherosclerosis was associated with the presence of AD and vascular of origin and the association was particularly strong in those with the APOE ε4 genotype (Hofman et al., 1997). However, in a later analysis, the association had disappeared (Slooter et al., 1999).

2.5.1.4. Apolipoprotein E and mortality

Since APOE gene has been associated with the occurrence of several diseases, it might lead to an earlier death particularly in association with AD and cardiovascular diseases (Utermann et al., 1984; Mahley 1988; Corder et al., 1993; Wilson et al., 1994; Stengård et al., 1995; Stengård et al., 1996; Farrer et al., 1997; Vogt et al., 1997; Lahiri, 2004; Lewis and Brunner, 2004). In older Finnish men, there was an excess of ε4 allele in the men who died of coronary heart disease (CHD) (Stengård et al., 1995). The ε2 allele which is associated with lower LDL cholesterol levels is associated with both anti-atherogenic and atherogenic changes in the content and composition of plasma lipids (Utermann et al., 1975; Davignon et al., 1988; Davignon and Roy, 1993). The relative frequency of ε2 is lower in Finns who have a high CHD mortality (Stengård et al., 1996) and the frequency is higher in male octogenarians who have avoided CHD death (Davignon et al., 1988). In a recent study of subjects aged 75 years and over, death increased by 22% in those individuals with the ε4 allele and was 28% decreased in those carrying the ε2 allele. The protective effect of the ε2 allele was present only among women (Rosvall et al., 2008). There are several longitudinal studies in line with these findings i.e. an association between increased mortality and APOE ε4 allele (Corder et al., 1996; Tilvis et al., 1998; Hayden et al., 2005). However, there are also opposite results (Koivisto et al., 2000; Frisoni et al., 2001; Slooter et al., 2001).

2.5.2. Atrial fibrillation

2.5.2.1. Definition and prevalence of atrial fibrillation

AF is the most common clinically significant cardiac arrhythmia in the elderly. AF is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function. In the electrocardiogram (ECG), AF is characterized by the replacement of consistent P waves by rapid irregular fibrillatory waves, and a ventricular response when atrioventricular (AV) conduction is intact (Bellet, 1971). Several classification systems have been proposed for AF. Traditionally, the classification is based on ethiology, and distinguishes between valvular and nonvalvular AF. The nonvalvular form accounts for 50-80% of all AF (Dunn et al., 1986). One classification is based on ECG charasteristics (Bellet, 1971) and another is based on epicardial (Allessie et al., 1994) or endocavitar recording or noncontact mapping of atrial electrical activity.

The clinical presentation of AF may be paroxysmal or persistent (Fuster et al., 2006). Paroxysmal AF is diagnosed if the episodes stop spontaneously within seven days, but is regarded as persistent if electrical or pharmacological cardioversion is needed to stop the arrhythmia. Recurrent AF occurs when a patient experiences two or more episodes of the disorder, which could be paroxysmal or persistent in nature. Permanent AF occurs when a patient continues to experience the arrhythmia, when the cardioversion is not successful or deemed inappropriate (Lip and Tse, 2007).

The most powerful risk factor for AF is age (Flegel et al., 1987; Rich, 2009). The prevalence of AF increases sharply with advancing age (Feinberg et al., 1995) and may be greater in men (Fuster et al., 2001; Heeringa, et al., 2006). The prevalence of AF varies from 7.3% to 44.7% in individuals aged 80 years or older (Lake et al., 1989; Phillips et al. 1990; Furberg et al., 1994; Go et al., 2001; Freestone and Lip, 2003; Marini et al., 2004). Most persons with AF have associative cardiovascular disease or other systemic illness such as hypertension, congestive heart failure, or CHD (Kannell et al., 1982; Flegel et al., 1987; Benjamin et al., 1994; Krahn et al., 1995; Clark et al., 1997; Haïssaguerre et al., 1998). The wide variation in prevalence may be explained by

different populations and age-groups, or the diagnostic methods used. The lifetime risk for development of AF has been estimated to be approximately 1 in 4 (Lloyd-Jones et al., 2004).

2.5.2.2. Atrial fibrillation and stroke

AF is one of the major risk factors for stroke in the older people (Wolf et al., 1991a; Shinkawa et al., 1995; Jørgensen et al., 1996; Lin et al., 1996; Marini et al., 2004; Arboix et al., 2006; Béjot et al., 2009; Kannel and Benjamin, 2009) accounting for one fifth of hospitalizations for acute stroke in individuals aged 75 years and over (Lamassa et al., 2001). With or without an associated cardiac diagnosis, it is the most common cardiac diagnosis related to stroke (Caplan 1983; Broderick et al., 1992). The most important mechanism of stroke is cerebral emboli from the fibrillating left atrium and it is only rare associated with lacunar infarcts (Norrving and Staaf, 1991). AF also reduces cardiac output which may impair cerebral blood flow and, therefore, increase the risk of stroke (Upshaw, 1998).

The risk for stroke due to AF increases with age and the proportion of strokes attributable to AF has been estimated to be as high as 42.6% (Arboix et al., 2006). Anticoagulation with warfarin decreases the risk by 64% (Hart et al., 2007). The older stroke patients with AF are also more severely disabled and more likely to die than patients without AF (Kaarisalo et al., 1997). While the impact of hypertension, CHD, and cardiac failure on the risk of stroke seems to decline with advancing age, the impact of AF on stroke is persistent even up to the ninth decade of life (Wolf et al., 1991b). Some studies suggest that women with AF are at a higher risk for ischemic stroke (Fang et al., 2005; Marini et al., 2005) while others have not found any difference (Gage et al., 2001).

In addition to symptomatic strokes, up to 13-26% of patients with AF suffer from clinically silent cerebral infarcts which can be identified in a CT scan or at autopsy (Feinberg et al., 1990; Ezekowitz et al., 1995; Shinkawa et al., 1995). Silent infarcts are at least twice as common in people with AF as in those without this disease (Peterson et al., 1987; Kempster et al., 1988; Guidotti et al., 1990). Some studies suggest that AF is

more common in subjects showing periventricular white matter changes on magnetic resonance imaging (MRI) than in those without these changes (Räihä et al., 1993; De Leeuw et al., 2000).

2.5.2.3. Atrial fibrillation and cognition

Though the development of dementia is common after the diagnosis of first AF (Ott et al., 1997; Forti et al., 2007; Miyasaka et al, 2007; Puccio et al., 2009), the relationship between AF and cognition is complex and controversial. In the age group of 80-84 year olds, the incidence of dementia was 28.1 per 1000 person-year in men and 24.7 per 1000 person-year in women in the general population when compared with 58.3 per 1000 person-year in men and 55.8 per 1000 person-year in women in the AF cohort (Miyasaka et al., 2007). In some studies, AF predicted the development of PSD (Cencori et al., 1996; Intzitari et al., 1998; Barba et al., 2000) while in others no associations between AF and PSD have been found (Tatemichi et al., 1990; Pohjasvaara et al., 1998). It has also been suggested that AF is associated with poor cognitive performance even in the absence of clinical stroke (Farina et al., 1997; Ott et al., 1997; Kilander et al., 1998a; Sabatini et al., 2000; Tilvis et al., 2004; Elias et al., 2006) and the risk increased with advancing age (Miyasaka et al., 2007). The Rotterdam Study showed that dementia was twice as common in subjects with AF as in those without these symptoms. The association was stronger in those younger than 75-years and surprisingly also stronger for AD than for vascular dementia (Ott et al., 1997). It has also been reported that the risk of conversion of MCI to dementia is linked with AF (Ravaglia et al., 2006).

The relationship between AF and dementia has attracted many theories. It has been suggested that AF is associated with increased risk of asymptomatic “silent” cerebral infarction (Feinberg et al., 1990; Ezekowitz et al., 1995). An alternative haemodynamic mechanism could be beat-to-beat variability in cardiac cycle length causing variations in cerebral perfusion (Petersen et al., 1989). Many AF patients have also multiple comorbid conditions and may be at risk of cognitive dysfunction due to these concurrent pathologies (Patel et al., 2004).

2.5.2.4. Atrial fibrillation and mortality

Chronic AF is one of the major causes of overall mortality (Krahn et al., 1995; Benjamin et al., 1998; Stewart et al., 2002; Vidaillet et al., 2002; Freestone and Lip, 2003). The risk of cardiovascular death in subjects with AF is double that of controls in men and nearly three times higher in women (Kannel et al., 1982). One year mortality for AF varies from 30.5% to 63% (Lin et al., 1996; Dulli et al., 2003; Marini et al., 2005). In one study, AF diminished the female survival advantage over men (Benjamin et al., 1998).

In a recent study on non-demented subjects AF was associated with a relative hazard for mortality of 80% above that of the age-expected in the general population. In demented patients, the relative hazard of mortality was about three times that of age-expected (Miyasaka et al., 2007). Whether AF itself is a causal factor for mortality or a proxy for greater cardiovascular or other disease burden is still a matter for debate (Dries et al., 1998; Al-Khatib et al., 2001; Maisel and Stewenson 2003, Wang et al., 2003). AF itself is associated with increased mortality as a result of embolic conditions such as stroke and other cardiovascular causes (arrhythmias, congestive heart failure, and fatal myocardial infarctions) (Peters and Kienzle, 1988; Benjamin et al., 1998; Stewart et al., 2002). It is notable that older patients with AF have also other cardiac disorders and part of the increased mortality may be caused by the coexisting cardiac disorders.

2.5.3. Blood pressure

2.5.3.1. Definition of blood pressure

Blood pressure is defined as a measure of the force exerted by circulating blood on the walls of the main arteries. The highest pressure (systolic blood pressure, SBP) is created by the heart contracting (pumping blood outwards) and the lowest pressure (diastolic blood pressure, DBP) is measured as the heart fills with blood. Essential, primary, or idiopathic hypertension is defined as elevated BP in which secondary causes such as renovascular disease, renal failure, pheochromocytoma, aldosteronism, or other such

causes of secondary hypertension or mendelian forms (monogenic) are not present (WHO, 2008).

The most widely used criteria for hypertension are those defined by World Health Organization/International Society of Hypertension. The latest criteria from 2004 recommend the limits of 140 mmHg for SBP and 90 mmHg for DBP. For people with DM or with decreased renal function, the recommendations are <130 mmHg SBP and <80 mmHg DBP. The recommendations are the same for both the young and old (Whitworth and Chalmers, 2004). Standardization of BP measurement is challenging and there are problems related to equipment, measuring personnel, patients, environment and technique. The limits used in different studies for high BP have varied from 140/70 to 180/95 mmHg (Agüero-Torres et al., 1994; Yoshitake et al., 1995; Curb et al., 1996; Guo et al., 1996; Weijenberg et al., 1996; Starr et al., 1997; Chalmers 1998; Seux et al., 1998; Elias et al., 2003; Solfrizzi et al., 2004; Raffaitin et al., 2009). In subjects aged 85 and older, the prevalence of hypertension has been estimated to be as high as 71% (de Craen et al., 2003). Systolic hypertension is the predominant form of the hypertension in the elderly and increases linearly with age, while DBP increases up to the age of 50 and then declines (Burt et al., 1995). These changes are related to the decreased elasticity ans stiffening of large arteries as a consequence of arteriosclerosis.

2.5.3.2. Blood pressure and stroke

Hypertension is the most important risk factor for stroke and ischemic white matter lesions in both men and women, but it seems to attenuate with age (Román 1987; MacMahon et al., 1990; Eastern Stroke and Coronary Heart Disease Collaborative Research Group, 1998; Skoog, 1998c; de Leeuw et al., 1999; Chobanian et al., 2003; Hu et al., 2005; Lewington et al., 2007). The incidence of stroke seems to increase linearly in proportion to both SBP and DBP with the risk of first stroke increasing by more than one half for each 10 mmHg increase in DBP (MacMahon et al., 1990; Lewington et al., 2007). However, some other cohort data have demonstrated a J-shaped curve of the association between BP and stroke (Farnett et al., 1991; D'Agostino et al., 1994; Kannel et al., 1997).

In subjects aged 80-89 years, the risk of stroke for each 20 mmHg lower than the usual SBP is 33% lower while in subjects aged 50-59 years the risk of stroke is 63% lower (Lewington et al., 2007). In one study, the 10-year stroke risk in subjects aged 60 years and older was 19.6% being greater in patients with diagnosed hypertension than in patients with elevated BP without previously diagnosed hypertension (Redòn et al., 2007). In one large meta-analysis in subjects with a mean age 63 years, a 10 mmHg reduction in SBP was associated with a risk reduction in stroke of 31% (Lawes et al., 2004). In a recent study examining subjects aged 80 years and over, lowering SBP (≥160 mmHg) or DBP (90-109 mmHg) to below 150 mmHg SBP and 80 mmHg DBP respectively, it was found that the changes were associated with a 30% reduced risk of the fatal and non-fatal stroke (Beckett et al., 2008).

2.5.3.3. Blood pressure and cognition

The association between hypertension and cognition has been studied extensively and it seems that both high and low BPs play a part in the development and progression of cognitive impairment and dementia, depending on age (Qiu et al., 2005). The association between high BP at midlife with late-life impaired cognitive function or dementia is well established (Kilander et al., 1998b; Kilander et al., 2000; Launer et al., 2000; Kivipelto et al., 2001ab; Wu et al., 2003; Whitmer et al., 2005). In the end of follow-up of Honolulu-Asia Aging study, subjects with elevated SBP (≥160 mmHg) at midlife had lower brain weight, increased number of neuritic plaques in both neocortex and hippocampus, increased number of neurofibrillary tangle, and worse hippocampal atrophy than controls (Petrovich et al., 2000; Korf et al., 2004). Recent studies suggest that use of hypertensive treatment decreases the risk of dementia in subjects less than 76 years of age (Haag et al., 2009) and may decrease the development of AD pathology in the brain (Hoffman et al., 2009).

Cross sectional studies in very old people have detected an association between both high BP (Starr et al., 1993; Cacciatore et al., 1997; Budge et al., 2002; Kuo et al., 2004) and low BP (Guo et al., 1996; Rockwood et al., 1996; Guo et al., 1997a; Morris et al.,

2000; Pandav et al., 2003; Kähönen-Väre et al., 2004) and cognitive impairment or dementia. Also a U-shaped association between BP and poor cognitive performance has been reported (Waldstein et al., 2005) or no association between BP and cognition (Farmer et al., 1987; Scherr et al., 1991; Ueda et al., 1992; Kuusisto et al., 1997) (Table 2). The most common criterion for hypertension used in these studies has been the cutoff point of SBP 160 mmHg or previously diagnosed hypertension.

Longitudinal studies in the very old have reported conflicting results (Table 3). An association between baseline high BP or diagnosed hypertension with impaired cognition in the followup has been reported in many studies (Haan et al., 1999; Harrington et al., 2000; Elias et al., 2003; Piguet et al., 2003; Waldstein et al., 2005; Reitz et al., 2007). Skoog et al. followed subjects aged 70 years and older for 15 years and found that those with high SBP or high DBP at baseline had a higher risk for developing dementia, but paradoxically they experienced a fall in BP during several years before the onset of dementia (Skoog et al., 1996). No association (Cervilla et al., 2000; Hebert et al., 2004; Tervo et al., 2004; Solfrizzi et al., 2004; Shah et al., 2006; Raffaitin et al., 2009), or a U-shaped association (Guo et al., 1997b; Glynn et al., 1999; Bohannon et al., 2002) with BP and dementia have also been reported. One study with very old subjects (75-101 years old) reported that low BP associated with poor cognition (Waldstein et al., 2005). A recent study on subjects aged 80 years or over showed that high SBP was associated with better cognitive function at the baseline and in the longitudinal assessment while low SBP was associated with cognitive decline and dementia (Nilsson et al., 2007).

There are several possible mechanisms explaining the the association between BP and cognitive impairment or dementia. Hypertension can promote cerebral ischemic lesions revealed as white matter hyperintensities in MRI, leading to cognitive impairment and dementia (Francheschi, 1982; Mazzhuci et al., 1986; Farmer et al. 1990; Starr et al., 1992; Elias et al., 1993; Starr et al., 1993; Kalaria et al., 2000; Vermeer et al., 2003; de Leeuw et al., 2004). Chronic and episodic cerebral hypoperfusion is suspected to be one of the pathways linking vascular disorders to dementia both VaD and AD (de la Torre et

al., 2004). Orthostatic hypotension has also been associated with a cognitive decline (Passant et al., 1997). However, dementing diseases like AD may themselves cause a reduction in BP (Guo et al, 1996) and a failure to maintain BP may be an expression of brain lesions in prefrontal autonomic centers accompanying AD disease, resulting in central disregulation of BP (Skoog et al., 1997).

Table 2. Blood pressure and cognition in the older people, cross section studies.

Author	Study population N, age (years)	Main results (BP mmHg)
Farmer et al., 1987	2123, 55-89	BP had no association with cognition
Scherr et al., 1991	3627, ≥65	BP had no association
Ueda et al., 1992	887, ≥65	Hypertension (≥160/95) associated with VaD not with AD
Starr et al., 1993	598, ≥79	High BP (>181/95) associated with low MMSE
Launer et al., 1995	3735, mean age 78	Low BP (SBP≥160mmHg vs. <110 mmHg) associated with poor cognition
Guo et al., 1996	1642, ≥75	High BP (≥140/75) associated with dementia and AD
Guo et al., 1997a	1736, ≥75	Low BP associated with poor cognitive function
Kilander et al., 1998a	999 men 69-75	Each 1Sd increase in DBP was associated with OR 1.45 for low cognitive function
Kuusisto et al., 1997	980, 69-78 years	BP did not associate with AD
Di Carlo et al., 2000	3425, 65-84 years	History of hypertension (≥140/90) did not associate with cognition
Harrington et al., 2000	107, 70-89	Hypertensive group (160-179/90-99) had poorer cognition
Morris et al., 2000	709, ≥65	Low BP (<130/70) associated with AD
Stewart et al., 2001	278, 55-75	Diagnosed hypertension associated with poor cognition

Author	Study population N, age (years)	Main results (BP mmHg)
Budge et al., 2002	158, 60-91	High SBP associated with lower MMSE and lower CAMCOG
Morris et al., 2002	5816, ≥65	U-shaped association with poor cognition
Kähönen-Väre et al., 2004	650, 75, 80, 85	History of hypertension had no association with cognition. Low BP associated with poor cognition
Kuo et al., 2004	70, ≥65	High SBP (>145) associated with impairment in executive function
Waldstein et al., 2005	847, 60-96	DBP had U-shaped association with cognition

Table 3. Longitudinal studies with blood pressure and cognition in the older people.

Author	Study population, N, age (years)	Follow-up (years)	Main results
Yoshitake et al., 1995	828, 65-98	7	≥160/90 mmHg associated with VaD, but not with AD
Skoog et al., 1996	382, >70	15	High SBP and DBP at the baseline were higher in those who developed
Guo et al., 1997b	1736, ≥75	3	U-shaped association
Haan et al., 1999	5888, ≥65	7	Each 22mmHg increase in SBP was related to 0.96 point decline in MMSE
Starr et al., 1997	603, >69	4	SBP≥160mmHg associated with cognitive decline
Brayne et al., 1998	376, ≥75	2-4	History of hypertension did not associate with dementia
Glynn et al., 1999	3657, ≥65	9	130 <SBP≥160 U-shaped association
Morris et al., 2001	378, ≥65	13	Cut off points SBP≥160 vs 130-139, DBP<70 vs >90. Increased incidence of dementia and AD with low SBP and DBP
Bohannon et al., 2002	3292, ≥65	3	U-shaped association with SBP
Posner et al., 2002	1259, ≥65	7	History of hypertension did not associate with AD
Elias et al., 2003	1423, 55-88	4-6	High BP (≥140/90) had positive association with cognitive decline
Piguet et al., 2003	377, ≥75	6	High BP (>140/90) had greater decline in MMSE scores over 6 years

Author	Study population, N, age (years)	Follow-up (years)	Main results
Qiu et al., 2003	1270, ≥75	5	SBP>180 vs 141-180, RR for dementia 1.4 (95% CI 0.9-2.4) DBP<70 vs >70-89, RR for dementia 1.8 (95% CI 1.2-2.6)
Verghese et al., 2003	488, ≥75	6-7	SBP 140-179 vs 111-139, RR for dementia 0.6 (95% CI 0.3-4.1) DBP <70 vs >90, RR for dementia 2.1 (95% CI 1.1-3.8)
Solfrizzi et al., 2004	1445, 65-84	3-5	BP ≥140/90 or diagnosed hypertension did not associate with MCI dementia
Tervo et al., 2004	806, 60-76	3	BP ≥160/95 did not associate with MCI
Kuo et al., 2004	1736, 65-94	2	Positive association with cognitive decline
Waldstein et al., 2005	847, 60-96	11	High SBP associated with poor cognitive performance
Shah et al., 2006	990, mean age75	6	Continuous BP no association with AD
Li et al., 2007	2356, 65+	2	SBP<160 associated with dementia in the age group <75, but not in older age group
Nilsson et al., 2007	599, mean age 80+	4	Low SBP associated with increased risk of cognitive impairment
Reitz et al., 2007	918, ≥65	7	>140/90 or history of hypertension associated with MCI
Raffaitin et al., 2009	8087, ≥65	4	>130/85 no association between hypertension and developing dementia

2.5.3.4. Blood pressure and mortality

Low BP has been associated with increased mortality among the very old in many studies (Table 4). The Kungsholmen study reported an increased relative risk of death in subjects aged 75 years and over with low SBP and DBP (Guo et al., 1997c). In other studies, the mortality was highest in those with the SBP below 120 mmHg, or the DBP below 70 mmHg and lowest in subjects with BP over 160 mmH or DBP over 90 mmHg (Rajala et al., 1983; Mattila et al., 1988). The greatest five-year survival has been reported with the SBP over 180 mmHg or the DBP over 90 mmHg (Hakala et al., 1997) and six years survival with BP over 160/90 mmHg compared to subjects with low BP (Jensen et al., 1997). Also a history of hypertension combined with current low BP (<140/70 mmHg) has been associated with mortality (van Bemmel et al., 2006). One recent large study of the Veterans Affairs has confirmed these previous findings. A large number for a total of 59207, hypertensive patients aged 80 years and over were followed until their death or about five years. The results showed that patients with low BP had lower survival than those with high BP (Oates et al., 2007). However, one large study found an association with low SBP (<130 mmHg) with better survival compared to high SBP (≥180 mmHg) in men aged 65-84 years old. Also men with high DBP (≥90 mmHg) had the greatest survival, though no such association was found in women (Satish et al., 2001).

Some studies have suggested that the association between BP and mortality is a J- or U-shaped curve. In the Framingham study, the correlation between SBP and both cardiovascular and all-cause mortality was U-shaped (Kannel et al., 1997). In the Established Populations for Epidemiological Studies of the Elderly Study (EPESE) including subjects aged 65 years and over, there was a J-shaped curve in the association between DBP and survival (Blazer et al., 2001). In the Helsinki Ageing Study, the association with DBP and survival was J-shaped in the age-group of 75 year olds, but linear in the 80- and the 85 year olds (Hakala et al., 1997). The most recently published study showed that in subjects aged 85 years and over, low SBP was associated with greater mortality and the optimal SBP in that age group was above 140 mmHg and there was a tendency toward a U-shaped mortality curve (Molander et al., 2008).

Author	**Study population N Age, years**	**Best survival BP (mmHg)**
Mattila et al., 1988	561,85+	>160/>90
Langer et al., 1989, Subanalysis	2270, 65+ 454, 75+	DBP≥95, association only with men
Starr et al., 1996	603, 75-85	>180/>90
Hakala et al., 1997	521, 75/80/85	>180/>90
Kannel et al., 1997	491, 75+	men SBP<120 or ≥180
Guo et al., 1997c	1810, 75+	>130/>75
Boshuizen et al., 1998	835, 85+	>200/>100
Satish et al., 2001, Subanalysis	12802, 65+ 1088, 85+	men SBP≥180 men DBP>90
van Bemmel et al., 2006	599, 85+	BP>140/70
Oates et al., 2007	4071, 80+	≥140/≥90
Molander et al., 2008	348, 85+	SBP >140 U-shaped

Table 4. Blood pressure and mortality in older people.

2.5.4. Diabetes mellitus

2.5.4.1. Definition and prevalence of diabetes mellitus

DM is a chronic metabolic disease caused by an inherited and/or acquired deficiency in production of insulin by the pancreas, or by the ineffectiveness of the insulin produced. The prevalence of DM is on the increase due to population growth, aging, urbanization, life style changes and the increasing prevalence of obesity and inactivity (Zimmet et al., 2001; Flegal et al., 2002; Katzmarzyk and Mason 2006; Ogden et al., 2006). Also improved survival of people with DM may also contribute to the prevalence of the disease (Stovring et al., 2003; Thomas et al., 2003; Lipscombe and Hux, 2007). The increase in DM has been mainly attributed to a rise in the numbers of new cases of type 2 diabetes (American Diabetes Association, 2005). The prevalence of DM among people aged 80 or over has been estimated to be 15%-20% (Wild et al., 2004). In a recent study of individuals aged ≥75 years, it was claimed that the prevalence of DM was 9.4% for men and 6.8% for women (Hewitt et al., 2009).

2.5.4.2. Diabetes mellitus and stroke

DM is a well established and independent risk factor for stroke (Jarret, 1989; Stegmayr and Asplund, 1995; Simons et al., 1996; Jamrozik et al., 2000; Hu et al., 2005; Air and Kissela, 2007; Rincon et al., 2009) and it doubles the rate of recurrent stroke (Hankey et al., 1998). The elevated relative risk for stroke has been estimated to range from 1.8- to nearly 6-fold (Burchfiel et al., 1994). Stroke patients with DM have also a poorer prognosis with higher morbidity and mortality (Sprafka et al., 1994; Stegmayr and Asplund., 1995; Kaarisalo et al., 2005). An increased risk of suffering lacunar infarctions with DM has been reported (Korf et al., 2006). DM increases also the prevalence of other strokerelated atherogenic risk factors, notably hypertension, obesity, and abnormal blood lipids as well as atherosclerosis itself (Pyörälä et al., 1987). Hyperglycemia is an independent risk factor for stroke (Iso et al., 2004b; Kissela et al., 2005).

2.5.4.3. Diabetes mellitus and cognition

The association between DM and cognitive impairment is complex. DM has been associated with cognitive decline in many studies (Elias et al., 1997; Fontbonne et al., 2001; Knopman et al., 2001; Arvantakis et al., 2004; Hassing et al., 2004; Whitmer et al., 2005), but not in all (Breteler et al., 1994; Bourdel-Marchasson et al., 1997; van den Berg, 2006). DM seems to be a risk factor for VaD (Luchsinger et al., 2001; Hassing et al., 2002; Peila et al., 2002; MacKnight et al., 2002; Xu et al, 2004; Korf et al., 2006). In the Kungsholmen project, DM increased the risk of vascular dementia independent of other vascular factors (Xu et al., 2004). Moreover, DM and high SBP (≥180 mmHg) had a synergistic effect on the risk of any dementia. DM is known to be associated with small vessel disease such as white matter lesions and large vessel disease such as infarction (Mast et al., 1995) and dementia may be attributable to these vascular changes, while the risk of VaD increases steeply with stroke (Tatemichi et al., 1992; Tatemichi et al., 1994b). Also other diseases such as hypertension and hyperlipidemia have been found to be involved in the relationship between DM and VaD (Gorelick, 1997; Moroney et al., 1999).

The association between DM and AD is less clear. Some large studies have found an association between these two entities (Leibson et al., 1997; Brayne et al., 1998; Peila et al., 2002). In the longitudinal Rotterdam Study, DM almost doubled (RR 1.9 CI 95% 1.2-3.1) the risk of AD (Ott et al., 1999). In the Framingham Study, DM did not increase the risk of incident AD, but DM was a risk factor for AD in the absence of other vascular risk factors, such as homocysteine level or APOE ε4 allele (Akomolafe et al., 2006). However, no association between DM and AD has been found in many clinical studies (Yoshitake et al., 1995; Luchsinger et al., 2001; Hassing et al., 2002; MacKnight et al., 2002; Xu et al., 2004) or between DM and plaques or neurofibrillary tangles in neuropathological studies (Heitner et al., 1997; Peila et al., 2002). Other studies have hinted at an association between DM and whole-brain atrophy or hippocampal atrophy (den Heijer et al., 2003; Korf et al., 2007).

2.5.4.4. Diabetes mellitus and mortality

Since subjects with DM have a higher incidence of atherosclerotic cardiovascular disease (CVD) they suffer greater cardiovascular mortality (Stamler et al., 1993; Haffner et al., 1998; Thomas et al., 2003), stroke-related mortality (Tuomilehto et al., 1996; Hu et al., 2005), and all-cause mortality (Wei et al., 1998; Morgan et al., 2000). In the period between 1995 and 2005 there was a 25% decline in mortality in subjects with DM (Stovring et al., 2003; Thomas et al., 2003; McBean et al., 2004; Lipscombe and Hux, 2007) due to improved treatment and better screening. The overall and cardiovascular mortality rates are 2-4 times higher in type 2 diabetic patients than in nondiabetic subjects (Panzram et al., 1987; Stengård et al., 1992; Balkau et al., 1997). Even nondiabetic levels of hyperglycemia, as observed in impaired fasting glucose and impaired glucose tolerance are claimed to associate with an elevated risk of CVD and premature mortality (Unwin et al., 2002; Gerstein et al., 2005). Abnormal glucose metabolism has been thought to contribute to CVD deaths (Barr et al., 2007). The increased mortality was claimed to be due DM itself, poor metabolic control, other concomitant diseases, or other factors (Hoogeveen et al., 2000).

2.5.5. Dyslipidemia

2.5.5.1. Definition of dyslipidemia

Dyslipidemia is one of the major modifiable cardiovascular disease risk factors in middle-aged people, though its significance in older people is still on debate. One central feature of the pathogenesis of atherosclerosis is the deposition of cholesterol in the arterial wall (Levine et al., 1995; Williams and Tabas, 1995). The diagnosis of dyslipidemia requires analyzing at least two serum samples. In dyslipidemia, total cholesterol is >5.0 mmol/l, high density lipoprotein (HDL) is <1.0 mmol/l, low density lipoprotein (LDL) is >3 mmol/l, or triglycerides (TGC) is >2.0 mmol/l (De Backer et al., 2003). Mean HDL cholesterol varies little with age and levels are consistently higher for older women than for men (Kannel, 1988; Laurenzi and Mancini, 1988;

Ettinger et al., 1992; Winder et al., 1996). However, serum total cholesterol level decreases with age, particularly in the very old (Hershkopf et al., 1982; Ettinger et al., 1992; Winder et al., 1996; Nilsson et al., 2003). This phenomenon is more pronounced in men than women (Kannel, 1988; Laurenzi and Mancini, 1988). In the group aged over 85 years cholesterol levels are at their lowest (Schatz et al., 2001). The reasons for the decline in plasma cholesterol with age may be related to changes in nutrient intake, body weight and the presence of chronic illnesses that influence cholesterol levels (Harris et al., 1990; Nilsson et al., 2003). Other conditions commonly consireded as the normal ageing process, such as progressive reduction of cholesterol synthesis in the liver, concomitant diseases of different organs or reduced absorption from the gut may also lower the cholesterol levels (Gylling et al., 1994; Nilsson et al., 2003).

2.5.5.2. Dyslipidemia and stroke

While hypercholesterolemia is an important modifiable risk factor for CHD, the relation between serum total cholesterol and stroke remains unclear and conflicting. Elevated cholesterol levels have been found to be a risk factor for stroke in many studies (Salonen and Puska, 1983; Iso et al., 1989; Qizilbash et al., 1991; Benfante et al., 1994; Hachinski et al., 1996) whereas other studies have reported no association between high cholesterol and stroke (Prospective Studies Collaboration, 1995; Pedro-Botet et al., 1992; Sridharan, 1992; Simons et al., 1998; Shahar et al., 2003; Zhang et al., 2009). The low serum total cholesterol levels have been associated with fatal hemorrhagic stroke (Ariesen et al., 2003). However, this finding has been stated to be as an artifact since severe and chronic illnesses may reduce LDL levels (Amarenco et al., 2004). Most studies have reported an inverse association between HDL and ischemic stroke (Gordon et al., 1981; Pedro-Botet et al., 1992; Sridharan 1992; Simons et al., 1998; Lindenstrøm et al., 1994). The association between serum TGC levels and ischemic stroke is still a matter of debate. Both positive associations and no associations have been reported between TGC levels and ischemic stroke (Rhoads et al., 1983; Salonen and Puska, 1983; Iso et al., 1989; Perdo-Botet et al., 1992; Lindenstrøm et al., 1994).

Atherosclerosis is the primary pathological condition accounting for atherothrombotic brain infarction and hyperlipidemia correlates with the risk for cerebrovascular atherosclerosis with advancing age. Atherosclerosis of extracranial or intracranial arteries accounts for a substantial proportion of clinical ischemic strokes due to artery-to artery embolization of plaque-associated thrombi or distal atherothrombotic occlusion (Tell et al., 1988).

Several clinical trials and meta-analyses have shown clearly the beneficial effects of using statins in reducing cardiovascular morbidity and mortality in patients with CVD (Law et al., 2003; Baigent et al., 2005; Wei et al., 2006). Statins may reduce stroke risk 17%-31% (Blauw et al., 1997; Goldstein and Hankey, 2006). However, the data in treatment of older people is still sparse and findings are inconsistent (Abramson and Wright, 2007; Robinson et al., 2007).

2.5.5.3. Dyslipidemia and cognition

The studies of the association between cholesterol and dementia have reported conflicting results. High levels of total cholesterol and high LDL has been associated with both an increased (Notkola et al., 1998; Kivipelto et al., 2001ab; Lesser et al., 2001) and decreased risk (Romas et al., 1999; Piguet et al., 2003; Reitz et al., 2004; Mielke et al., 2005) of AD. Other studies have found no association between dyslipidemia and cognition (Postiglione et al., 1989; Yoshitake et al., 1995; Kalmijn et al., 2000; van Exel et al., 2002; Nilsson et al., 2003; Tan et al., 2003; Fischer et al., 2006). There may be several reasons for the results. A high cholesterol level in late life may be an indicator of better health status (Weverling-Rijnsburger et al., 1997; Beckett et al., 2000). There also may be a selection bias with those who survive to old age. It has been also shown that cholesterol levels decrease when cognition begins to decline (Kim et al., 2002) which may explain the low cholesterol levels in subjects already diagnosed with AD (Anstey et al., 2008).

Cholesterol plays an important role in the amyloid pathogenesis in AD (Simons et al., 1998; Olesen and Dagø, 2000) via its association with apoE and the APOE ε4 allele with increased risk and earlier onset of atherosclerosis and coronary artery disease

(Davignon et al., 1988; Kuusi et al., 1989). In a population based autopsy study, a strong association of late-life HDL levels with the number of neuritic plaques and neurofibrillary tangles was found (Launer et al., 2001). In another autopsy study, serum high cholesterol levels were an early risk factor for the development of Alzheimer amyloid pathology (Pappolla et al., 2003).

Few prospective cohort studies have investigated the relationship between lipid levels and the incidence of VaD. A recent meta-analysis found no evidence in support of an association between high serum total cholesterol levels with AD or any dementia. However, there was a consistent association detected between midlife high cholesterol and late life AD or any dementia (Anstey et al., 2008).

2.5.5.4. Dyslipidemia and mortality

The increased risk for cardiovascular heart disease and mortality from coronary heart disease with high cholesterol level has been reported in many studies (Laakso et al., 1993; Song et al., 2000; Okamura et al., 2007; Zhang et al., 2009). In a recent meta-analysis the relationship between cholesterol and death was significant in all ages and a 1 mmol/L reduction in total cholesterol lead to about a third lower ischemic heart disease (IHD) mortality. The ratio of total to HDL cholesterol seems to be a more informative predictor for IHD mortality than total cholesterol, HDL, or non-HDL cholesterol levels. Total cholesterol was a strongly positive risk factor for IDH mortality also in old age. The absolute difference in the annual risk of IHD death for a 1 mmol/L difference in total cholesterol was about ten times greater at 80-89 years than at 40-49 years of age. High HDL cholesterol levels were approximately independently associated with lower IHD mortality (Prospective Studies Collaboration, 2007). In some studies in elderly subjects, low HDL has increased mortality (Zimetbaum et al., 1992; Weverling-Rijnsburger et al., 2003). However, in the elderly, a negative association between cholesterol and stroke mortality there has been found (Prospective Studies Collaboration, 2007) or alternatively no increase in mortality with high total cholesterol or with high LDL (Nilsson et al., 2009). In a recent study examining very old patients aged 85+/-7 years low total cholesterol and HDL cholesterol predicted total mortality

though these have been more indicative of malnutrition/ chronic illness/frailty (Vischer et al., 2009).

There are still many questions concerning the cholesterol and mortality in the very old. The influence of high cholesterol levels on mortality seems to diminish with advancing age (Shipley et al., 1991; Krumholz et al., 1994) and higher serum total cholesterol levels have been associated with longevity in people aged 80 years and over (Weverling-Rijnsburger et al., 1997; Schatz et al., 2001). A U-shape association between high cholesterol level and mortality has also been reported in the very old (Jacobs et al., 1992).

3. AIMS OF THE STUDY

The aim of the present study was to examine vascular risk factors in the very old, particularly their influence on mortality and dementia. The specific aims were

1) To investigate the association between APOE allele, blood pressure and cardiac arrhythmias. (Study I)
2. To investigate the association between vascular risk factors, particularly blood pressure and all-cause mortality. (Study II)
3. To investigate the association between atrial fibrillation and dementia and brain pathology. (Study III)
4. To investigate the relationship between vascular risk factors, such as DM, BP, lipids, homocysteine and incident dementia. (Study IV)

4. SUBJECTS AND METHODS

4.1. Study population

The Vantaa 85+ Study is a prospective, longitudinal population based study including all residents whether living in institutions or at home in the City of Vantaa and aged 85 years or over (N=601) on April 1st, 1991. The baseline final cohort included 553 (92%) individuals and the baseline clinical examinations took place between the 1st April 1991 and the 12th March 1992. The study flow chart is shown in figure 1. The follow-up evaluations were conducted in 1994, 1996, and 1999. The vast majority of participants (n=479) died during the follow-up and on April 1 2000 there were only 42 subjects still alive. Over half of the baseline study population had been autopsied by 31st March 2001.

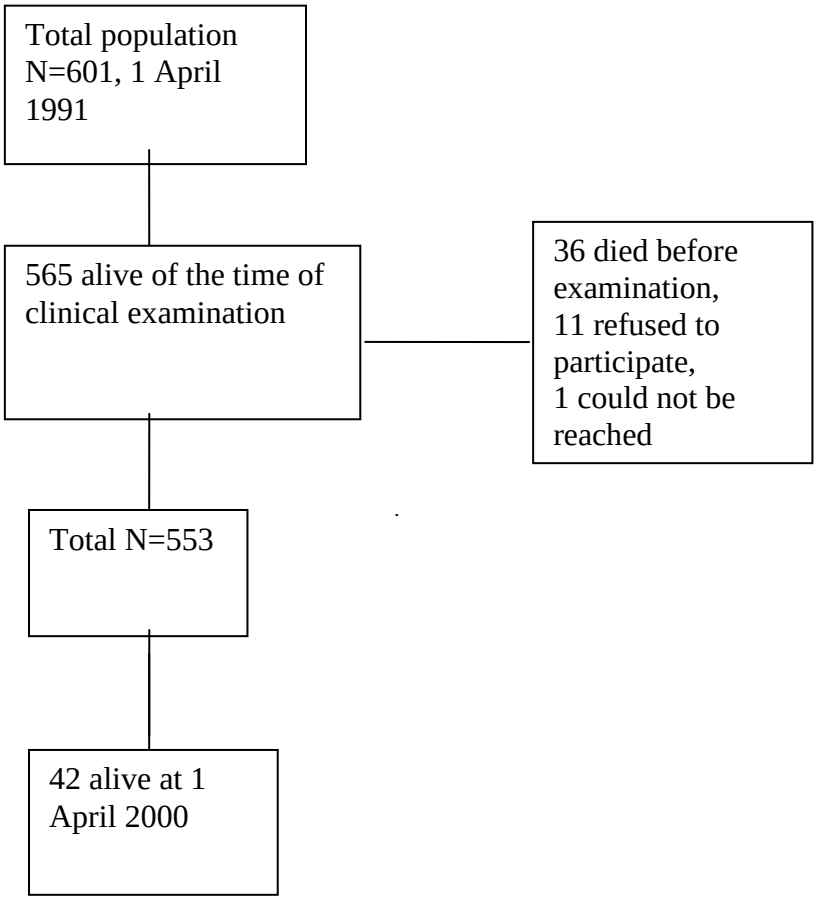

Figure 1. Study flow chart.

4.2. Methods

4.2.1. Clinical investigation

The evaluation included an interview by a trained nurse and clinical examination performed by a physician. The interview was conducted using a structured questionnaire consisting of questions concerning health, health-related behaviour, and medication.

Information on medical history for each participant was verified from a computerized database containing all primary care health records. The use of medications was checked from the patient, relative and/or the institution and also from an electronic primary health care database. The history of clinically significant diseases was recorded from health records. The physical examination was made by a neurologist and it included cardiac auscultation, BP measurement and neurological examination.

4.2.2. Diagnosis of dementia and clinical stroke

Two neurologists made the dementia diagnosis in consensus. The diagnosis of dementia was made by using the DSM-III R criteria (APA, 1987). Mini-Mental State Examination (MMSE) (Folstein and Folstein, 1975), Short Portable Mental Status Questionnaire (SPMSQ) (Pfeiffer, 1975), the Clinical Dementia Rating (CDR) (Hughes et al., 1982), Activities of Daily Living (ADL) (Katz et al., 1963) and Instrumental Activities of Daily Living (IADL) (Lawton and Brody, 1969) –scales were used to determine the cognitive status and functional abilities.

The diagnosis of clinical stroke was based on the history of previous transient ischemic attack or stroke in the medical records and the presence of clinical neurological focal signs indicating previous stroke. We also included in the stroke group 27 subjects without any history of cerebrovascular disease who had focal signs indicative of stroke. These subjects had spastic hemiparesis with or without dysphasia and no other explanation for the neurological findings.

4.2.3. Blood pressure measurement

BP was measured only once, since part of the study subjects were severe demented or ill and it would have been unethical to measure the BP two or three times. White coat effect was diminshed since white coats were not usually used. BP measurements were taken using a calibrated mercury sphygmomanometer with a cuff of appropriate size on the right arm of the subject in an identical, standardized way. The study subjects had rested and remained seated for at least five minutes prior to the measurement. The BP of

bedridden subjects was measured in a recumbent position. SBP was divided into three groups: below 140 mmHg, 140-159 mmHg, and 160 mmHg or over. The categories for DBP were 80 mmHg or less, 80-89 mmHg and 90 mmHg or over, respectively. BP medication was checked from the in-patient register. The BP lowering medication was divided into five groups: 1) diuretics, 2) beta-blockers, 3) calcium antagonists, 4) angiotensin-converting enzyme inhibitors, 5) and other BP lowering medication, such as alpha-blockers and perifal vasodilatators.

4.2.4. Methods to define cardiac rhythm

Resting ECG and short ambulatory holter ECG were used. Laboratory personnel took ordinary twelve lead resting electrocardiograms. In addition, one hour ambulatory holter ECG with three exploring electrodes attached at approximately as V1, V2, and V5 was used. The electrodes were attached at the beginning of the visit and the recording lasted until the end of the visit. When AF was present, it was determined as whether it was continuous or paroxysmal. Other noted rhythms were sinus rhythm, atrial flutter, pacemaker rhythm, supraventricular beats, ventricular premature beats and pause.

4.2.5. Determining of apolipoprotein E genotype

Apolipoprotein E genotyping was done by using a combination of polymerase chain reaction (PCR) and a solid phase minisequencing technique (Syvänen et al., 1993; Miettinen et al., 1994).

4.2.6. Neuropathological assessment

From the original study population (n=601) 306 deceased individuals were autopsied by 31st March 2001. There was no selection bias since permission for the obduction was asked from all the relatives of the deceased persons. The brains were fixed in buffered 4% formalin for at least two weeks before the dissection. The gross and microscopical examinations were performed by one pathologist (T.P.) blinded to all clinical data. The

exact same dissection and examination protocol was used for each brain. Cavitary lesions or solid cerebral infarcts visible to the naked eye were identified by examination of the intact brain and from 1 cm thick coronal slices of the cerebral hemispheres, from 5 mm thick transverse slices of the brain stem and sagittal slices of the cerebellum. The size of each infarct was measured with a mm-scale with the maximal dimension being for size categorization. Infarcts affecting the cerebral cortex were categorized as cortical infarcts. Infarcts in the cerebral white matter and/or subcortical grey matter were included in the subcortical infarct group if they did not extend to the cerebral cortex. The group of other infarcts included macroscopical ischemic lesions within the brain stem or cerebellum. All these lesions were subsequently histologically ascertained to be infarcts.

Paraffin sections were cut at a thickness of 8 micrometer for staining with methenamine silver Bodian stain for neurofibrillary tangles (Kondoh et al., 1993) and with a modified Bielschwsky method for neuritic plaques. Samples were obtained from the middle frontal, superior temporal, and middle temporal gyri, and inferior parietal lobule according to the protocol of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) for the estimation of the β-amyloid protein load in the neocortex. Tissue blocks recommended for neuropathological staging of the neurofibrillary changes were obtained from the entorhinal cortex at the level of the mamillary bodies, from the hippocampus at the level of the lateral geniculate body, and from the occipital lobe, so that the striate area, parastriate field and peristriate region were all represented in the same specimen. The tissue blocks were embedded in polyethylene glycol 1000, and then cut at a thickness of 80 μm for free floating staining with the Gallyas silver method for evaluating neurofibrillary pathology.

4.2.7. Statistical analysis

SPSS for Windows was used in all the analyse. The association between death and BP was analysed with Cox proportional hazard model adjusted for age, sex, education, underlying concomitant diseases (hypertension, myocardial infarction, congestive heart

failure, arteriosclerosis, DM, cancer, dementia, stroke, depression) and other confounding factors such as smoking, alcohol consumption, blood pressure lowering medication, functional status (independent in daily living or not) and their interactions. All terms were inserted in the model and the terms of lowest statistical significance were manually stepwise rejected. If a major term was to be removed but was a member of an interaction term, it was left in the model. Kaplan-Meier life-table analysis was also performed. The associations between risk factors and incident stroke or dementia were analyzed with Cox proportional hazards model adjusted for age, sex, and underlying concomitant diseases (hypertension, myocardial infarction, congestive heart failure, DM, AF).

Dichotomous variables were compared with chi-squared test, continuous variables with t-test or Kruskal-Wallis test. The odds ratios for different factors that might contribute to the baseline stroke or dementia were determined by logistic regression analysis with the backward Wald method. Age was divided into three age-groups: 85-89 years, 90-94 years and 95 years and over.

4.2.8. Ethical aspects

The study was reviewed and approved by the Ethics Committee of the city of Vantaa.

Informed consent was obtained from all participants that were capable of giving it or from a close relative. There were several ethical aspects to consider in this study. We examined the home-living persons in their homes because the transportation to the study place would have been very demanding for these very old people. When a previously undiagnosed illness was recognized, the patient was referred to the health care centre for further examinations. However, in 1991 when the study begun there was no available drug treatment for AD. However, if demented subjects had problems with living at home or behavioural problems, they were sent to the health care centre to receive symptomatic care. The guidelines for the use of anticoagulation in AF were radically different when the study begun than the current guidelines. In that time the anticoagulation treatment was not recommended to use in people over 80 years.

5. RESULTS

5.1. General characteristics of the study population

The mean age of the participants at baseline was 88.8 years (range 85-103.5 years) and 411 (79%) were female. No differences in average age or of sex distribution between the participants and the non-participants existed. 20.1% of total study population had had a stroke and 38.7% had dementia. Sociodemographic charasteristics of participants vs non-participants are shown in table 5.

The mean length of follow-up was 3.5 years. The longest follow-up was nine years. This study amounted altogether to 1817.9 person-years. In all, 479 died during the follow-up and by April the first on the year 2000 there were only 42 of our subjects still alive.

	Participants		**P**		**Non-Participants**	**P**
	Males	**Females**		**Total**	**Total**	
	N=110	**N=411**		**N=521**	**N=80**	
Mean age at baseline (SD)	88.5 (2.6)	88.9 (2.9)	0.2	88.8 (2.8)	88.6 (3.2)	0.5
85-89 years	80.9	76.6	0.6	77.5	75.0	0.8
90-94 years	16.4	19.0		18.5	21.2	
95 years and over	2.7	4.4		4.0	3.8	
Years of education (SD)	4.8 (3.7)	4.0 (2.7)	0.02	4.2	3.4	0.4
Living at home %	69.1	56.2	0.02	58.9	32.5	<0.001
Fully independent %	22.7	14.6	0.04	16.3	12.5	0.4

Table 5. Study characteristics.

5.2. APOE genotype and vascular risk factors (I)

High total serum cholesterol and high LDL cholesterol levels were associated with the presence of ε3/ε4 and ε4/ε4 alleles (Table 6). The levels of TGCs, or HDL cholesterol did not associate with APOE genotypes. No association was found between other vascular risk factors and APOE genotypes.

APOE genotype	mean cholesterol (±SD)	mean SBP	mean DBP (SD)
ε2/ε2	4.1 (1.2)	150 (14.1)	85 (7.1)
ε2/ε3	5.1 (1.2)	149 (25.5)	81 (12.0)
ε2/ε4	4.9 (0.9)	141 (32.1)	76 (13.4)
ε3/ε3	5.4 (1.3)	150 (28.1)	81 (13.2)
ε3/ε4	5.6 (1.2)	147 (27.3)	82 (12.3)
ε4/ε4	6.0 (2.1)	132 (27.3)	82 (8.1)
P	0.02	0.5	0.7

Table 6. APOE genotype and its association with total cholesterol and blood pressure.

5.3. Blood pressure and mortality (II)

The risk of death was highest in both men and women with low SBP <140 mmHg and this was seen particularly in the subjects who did not have dementia, cancer or a history of stroke. The association between SBP and death was most obvious during the first two follow-up years. The association between DBP and mortality was not significant after controlling the confounding factors.

In the multivariate analysis smoking, low functional status, cancer, dementia, stroke, and SBP <140 mmHg were associated with mortality (Table 7). Heart failure was not

associated with mortality in multivariate analysis, though it associated with mortality in univariate analysis. The risk of death was highest in the group of subjects with SBP <140 mmHg (p=0.02). Association between mortality and SBP ≥160 mm Hg was nonsignificant (HR 0.97, 95% CI 0.76-1.05). A history of hypertension or use of BP lowering medication did not associate significantly with mortality.

	HR	**CI 95%**
Smoking	1.97	1.09-3.52
Fully independet (ADL)	0.56	0.42-0.76
Cancer	1.42	1.00-2.03
Dementia	1.47	1.15-1.88
Stroke	1.80	1.37-2.37
SBP <140mmHg	1.35	1.04-1.74

Table 7. Factors associated with mortality in multivariate analysis.

5.4. Factors associated with clinical stroke (III)

At the baseline, 122 (22.1%) of the study subjects had AF and it associated with stroke and with neuropathologically verified macroscopical brain infarcts. Subjects with AF had more often clinical stroke (32%) than subjects without AF (16.7%) (p<0.001). Incident stroke during nine-year follow-up developed in 42 subjects who did not have clinical stroke at baseline. The Cox proportional hazards model which included age, sex, hypertension, cardiac insufficiency, myocardial infarct, DM, AF, and dementia at baseline showed that dementia at baseline associated significantly with the development of a new stroke during the follow up (HR 2.38 95% CI 1.20-4.73, p=0.013). AF at

baseline did not associate with incident stroke. Age, sex, hypertension, cardiac failure, myocardial infarct, or DM did not associate with incident stroke in the follow-up.

5.5. Factors associated with dementia (III, IV)

At the baseline there were 339 non-demented subjects. During the nine years of follow-up, 100 new dementia cases were diagnosed. At the first follow-up in 1994, there were 57 new dementia cases, in the second follow-up in 1996 there were 19 new dementia cases, and in 1999 i.e. the last follow-up there were 13 new dementia cases and 11 subjects had incident dementia before death (III). Subjects who had clinical stroke at baseline had also more often dementia at the baseline than the others (71.2% vs. 30.5%, $p<0.001$). At the baseline, dementia associated also with age and the presence of APOE ε4 allele but not with sex, education, DM, hypertension, cardiac failure, myocardial infarct, or AF (III). Table 8.

	OR	**95% CI**	**P**
90-94 years	1.85	1.08-3.17	0.024
95+	3.52	1.30-9.53	0.013
APOE ε4	2.71	1.69-4.32	<0.001
Clinical stroke	5.66	3.34-9.58	<0.001

Table 8. Factors associated with dementia at baseline in multivariate analysis.

Significant predictors for incident dementia during the follow-up were APOE ε4 allele and incident stroke in the Cox model adjusted with clinical vascular risk factors, sex and age (Table 9). However, when also laboratory markers (lipids and homocysteine) were included in the model, education, incident stroke, hypertension, and DM were

associated with incident dementia. Clinical stroke, blood lipids or homocysteine levels at baseline did not associate with developing dementia (IV).

	HR	**95 % CI**	**P**
APOE ε4	1.62	1.02-2.57,	0.042
New stroke	2.92	1.75-4.88	0.001

Table 9. Factors associated with incident dementia according to Cox proportional hazards regression analysis (subjects with dementia at baseline have been excluded, N=339 subjects).

	HR	**95 % CI**	**P**
Hypertension	0.59	0.34-1.00	0.049
Education	0.91	0.83-0.99	0.027
New first ever stroke	3.28	1.92-5.62	<0.001
Diabetes	1.73	1.04-2.88	0.035

Table 10. Factors that associated with developing dementia during the follow-up in Cox model (subjects with dementia at baseline have been excluded=339 subjects).

5.6. Brain pathology and dementia (III)

The neuropathological model showed that main predictors of dementia were beta amyloid load and the high number of small infarcts (<15 mm) but not with APOE genotype (Table 11). The Braak stage did not associate significantly with dementia; (OR 1.21, 95% CI 0.97-1.50, p=0.097). The protective factors from dementia were education and lack of subcortical vascular pathology (Table 12).

	OR	**95% CI**	**P**
beta-amyloid load	1.25	1.13-1.39	0.001
small infarcts <15 mm	1.34	1.10-1.65	0.004

Table 11. Neuropathologic factors predicting the dementia in the multiple regression analysis.

	OR	**95% CI**	**P**
Education	0.88	0.80-0.98	0.02
Lack of subcortical vascular pathology	0.39	0.15-1.01	0.05

Table 12. Significant factors to protect from dementia in the model including neuropathological factors.

6. DISCUSSION

The evaluation of vascular risk factors and their associations with mortality and dementia in the very old has become an important topic. Populations are becoming old and dementia and vascular diseases are common in old people. Vascular diseases are linked with dementia (Newman et al., 2005; Hayden et al., 2005; van Oijen et al., 2007, Knopman et al., 2009b) and thus primary prevention of the vascular diseases may lighten the burden of dementia. However, it seems that in very old individuals, the most burdensome vascular risk factors may be different than in their younger counterparts.

6.1. Methodological aspects

The present study had several strengths that make it possible to draw reliable conclusions. The participation rate was exceptionally high (92%), both institutionalised and home-dwelling people were included. The follow-up time was long, up to nine years, and collection of information of study subjects was quite complete.

However, there were several limitations in this study. The vascular risk factors in earlier life were not known. We were not able to further characterize the causes of dementia or clinical stroke in the study subjects due to several reasons. Neuroimaging was lacking in most subjects and no comprehensive neuropsychological examination was performed. However, a detailed neuropathological evaluation was performed in over half of the subjects and we were able to examine the neuropathological correlates of dementia. It is possible that we missed mild cognitive decline in some subjects since we focused cognitive decline severe enough to be defined as dementia. However, we were focusing only to the diagnosis of dementia. The median interval between the last observation and death was 367 days and it is possible that some subjects had developed dementia after the last observation. However, 72.1% of the subjects died in long term care institutions and information of cognitive status and function until death was available from their medical records. Nonetheless, it is possible that we missed some cases with mild dementia.

Although the presence of clinical stroke based on clinical examination and electronic primary health care database, not on brain imaging, neuropathological results confirmed that the subjects classified in the clinical stroke group did indeed have significant vascular pathology. However, it is apparent that subclinical vascular pathology may have been missed in some subjects.

Blood pressure measurements were made only once to avoid inconvenience to the study subjects since many of them were frail and had severe dementia. The blood pressure measurement was made in a standardized way and subjects were sitting or in a recumbent position. The reliability of blood pressure measurement is as good as can be achieved in this kind of study. It is possible that higher BP in one measurement simply reflects better vascular reactibility and thus better organ function and reserves in oldest individuals. Higher BP would thus be a surrogate for younger biological age and therefore a sign of better prognosis. For practical reasons, a 24 or 48 -hour Holter analysis could not be included in the study protocol (and even these may have missed some cases of paroxysmal AF). The combination of a short-term Holter examination and the information obtained from the health records was used instead. We believe that the number of undetected cases is small but this remains a potential source of bias in our study. The blood lipids were not measured after fasting since the blood samples were collected at the same time when the subjects were examined. We were not able to evaluate the role of DM and hypertension in detail since reliable information on the duration and severity was not available in the health records.

6.2. Factors associated with mortality in the very old

The very old represent a selected group of individuals, and their risk factors for mortality seem to differ from those encountered in the younger population. The frequency of reporting common chronic illnesses on the death certificate have changed over time. In 1981, atherosclerosis was the fifth most common cause of death of the oldest old in America and dementia or AD was rearly ever mentioned. Since 1999, AD

has become one of the most common causes of death (Gorina and Lentzner, 2008). Stroke is the third leading cause of death in the Western world (Vernino et al., 2003).

Our results showed that dementia was a significant predictor for death. Previous studies have also indicated that dementia is a major cause for the mortality in the very old and it has been shown that 5-year mortality rate in persons aged 95 years and older is significantly higher in demented subjects than in cognitively intact subjects (Börjesson-Hanson et al., 2007). However, vascular risk factors and previous history of cardiovascular disease are associated with dementia mortality (Alonso et al., 2009). In one, quite recent study, AF, DM, previous stroke and smoking influenced long term survival in the very old though no relationship between hypertension and long term mortality was found (Kammerskaard and Olsen, 2006). Another study suggested that DM with heart disease, stroke or hypertension were common underlying causes of death (Gorina and Lentzner, 2008). Also markers such as CRP have been found as indicators for death in the very old (Strandberg and Tilvis, 2000; Strandberg et al., 2009). The presence of carotid plaques as a marker of atherosclerotic disease has also been found to predict mortality in the very old (Störk et al., 2006).

Some studies indicate that vascular risk factors may not be good predictors for mortality at old age and there may even be an inverse correlations, for example between mortality and cholesterol, BP, and body mass index (Schupf et al., 2005; Oates et al., 2007; Takata et al., 2007). In the present study of very old people aged 85 years and over, allcause mortality was associated with low SBP (<140 mmHg). However, there is still no consensus of the harms and benefits of the high BP in the very old people and the studies reporting the association between BP and mortality have shown highly inconsistent results (Hakala et al., 1997; Langer et al., 1989; Guzik et al., 1992; Glynn et al., 1995; Starr et al., 1996; Guo et al., 1997c; Kannel et al., 1997; Satish et al., 2001, van Bemmel et al., 2006). These controversial results may be due to the fact that the studies are often made in younger populations, or study populations have consisted of less old indiviuals and often the number of very old people has been limited. The association of hypertension with mortality in our cohort may be due to the mortality at younger age of those individuals with poorly controlled elevated BP. The limits of high BP and for defining hypertension in the different studies also vary extensively. Large

epidemiological studies including participants aged 75 years or older have reported an increased relative risk of death in subjects with both low SBP and DBP (Guo et al., 1996; Kannel et al., 1997).

The treatment of hypertension in very old people is still on debate. Several large trials showed that the benefit of treatment for high SBP on mortality was lost in the very old subjects (over 80 years), and mortality was actually higher in the treatment group. However, antihypertensive treatment prevented cardiovascular complications, stroke and cardiac end points (Amery et al., 1986; Staessen et al., 1998; Goodwin, 2003). A large meta-analysis suggested a significant benefit of treatment of hypertension and treated subjects had less strokes and cardiovascular events and heart failure (Gueyffier et al., 1999). Recently, large hypertension in the very elderly trial (HYVET) showed that antihypertensive treatment based on indapamide with or without perindopril reduced the risk of death from any cause 21% in people aged 80 years and over (Beckett et al., 2008).

Our study was population based study and we did not focus on the treatment of hypertension. It is thus impossible to draw any conclusions of the treatment of hypertension in very old people according to our study. However, this special population of very old people is highly fragile to the side-effects of antihypertensive medication or hypotension, too.

6.3. Stroke in the very old

Stroke incidence increases with age (Rothwell et al., 2005; Goldstein et al., 2006) and 70% of strokes are first events (American Heart Association, 2003). Most strokes (70%) occur in those aged over 70 years, and 38% of hospitalized patients with an ischemic stroke are subjects aged 80 years and over (Saposnik and Black, 2009). In subjects aged 90 years and over, stroke mortality is six times higher than in subjects aged <69 years. Very old people have also longer hospitalization, and are less likely to be discharged to their original place of residence after stroke (Saposnik and Black, 2009). Common vascular risk factors such as BP, DM or AF are well known risk factors for stroke also

in the elderly and the prevalence of vascular risk factors increases with age (Browner et al., 2001; Avendano et al., 2006; Garcia and Hylek, 2007). The present study showed that chronic AF associated with baseline clinical stroke as well as with macroscopical brain infarcts, particularly with multiple large ischemic lesions. However, AF did not associate with the incident clinical stroke during the followup. This may be due to the fact that the majority of strokes occur during the first three years after the development of AF (Harmsen et al., 2006) and cardioembolic strokes are often large and fatal. Since the presence of AF was examined only at the baseline, we could not estimate the incidence of AF during the follow up. Also silent strokes and subcortical vascular changes which may not be clinically diagnosed are very common in old people especially with hypertensive subjects (Longstreth et al., 2002; van Dijk et al., 2002; Giele et al., 2004; Basile et al., 2006; Sierra and Coca, 2006) and subjects with AF have silent infarcts twice as often as those without AF (Kempster et al., 1988; Feinberg et al., 1990; Guidotti et al., 1990).

Our results showed also that baseline dementia was associated with incident stroke during the follow up. These findings are in line with this were findings of the Kungsholmen project where mild dementia at baseline was associated with the development of a new stroke in the follow-up among subjects aged 75 years or over (Zhu et al., 2000). Cerebral amyloid angiopathy (CAA) is a characteristic feature in AD but CAA related vasculopathic cerebrovascular changes such as fibrinoid necrosis and microaneurysm formation are found also in subjects with VaD (Vonsattel et al., 1991). Intracerebral hemorrhage and microinfarcts have been associated with the presence of CAA (Mandybur, 1986; Chen et al., 2006). A recent study proposed that CAA may not be associated with conventional vascular risk factors (Kimberly et al., 2009).

6.4. Factors associated with dementia in the very old

Very old people are especially susceptible to cerebrovascular incidents and prone to suffer dementia after stroke (Liebetrau et al., 2003). Our study confirms the association between stroke and dementia in the very old. Baseline stroke was associated with baseline dementia and the development of first-ever stroke was associated with the

development of incident dementia during the follow-up. The association between stroke and dementia is complex and the direction of the association is unclear. Stroke may enhance cognitive decline in AD at the symptomatic level but it is also possible that stroke can precipitate pre-existing AD (Snowdon et al., 1997; Honig et al., 2003).
The association between APOE genotype and dementia is complex in the very old. Two large population studies with a study population 75 years and over and the mean follow-up time of 3.5 to 4 years (Payami et al., 1997; Qiu et al., 2006a) showed that the influence of the APOE genotype on the dementia is influenced by age. The association between APOE ε4 and dementia may be weaker in older individuals than in younger subjects. It is possible that the APOE genotype decreases the age of the onset of AD (Miech et al., 2002), which may influence the association in the very old population. We observed an association between dementia and APOE ε4 at the baseline, and APOE ε4 was also linked with incident dementia. However, no association between dementia and APOE genotype was found in multivariate analysis including the neuropathological factors. Many studies have detected a significant influence of APOE genotype on the extent of AD type pathology (Nagy et al., 1995; Polvikoski et al., 1995; Ohm et al., 1999; Ghebremedhin et al., 2001; Tiraboschi et al., 2004). The inclusion of confounding factors such as quantitative pathological estimates in the model seemed to abolish the independent relationship between dementia and APOE genotype in our cohort.

The association between education with dementia was also complex. This may be due to mixed etiology of cognitive decline in this selective population of the very old. No association between dementia and education was found in the baseline data. However, a high level of education appeared to be protective against the development of incident dementia during the follow-up. Previous studies have suggested that a high level of education is related with a lower incidence of dementia (Rocca et al., 1990; Katzman et al., 1993; Ott et al., 1995). A lesser education has also been found to associate with a much steeper decline in cognitive function as a function of age up to about 95 years (Butler et al., 1996). However, studies in the very old are rare and have reported conflicting results (Piquet et al., 2003; Ravaglia et al., 2006). It has been hypothesized that education influences the development of the brain and cognitive reserve (Scarmeas

and Stern, 2004; Whalley et al., 2004; Christensen et al., 2007) and this can compensate for the age-associated brain tissue loss and damage even at very old ages. Our study support this hypothesis since after controlling for brain pathology, low education associated with the dementia.

In contrast to some previous studies, there was no association between AF and dementia or AD pathology in the brain. Many studies have detected an association between AF and poor cognitive outcome (Farina et al., 1997; Kilander et al., 1998a; Miyasaka et al., 2007) which may partially be related with the confounding effect of stroke to cognition. A relationship between AF and poststroke dementia has been found in some (Barba et al., 2000) but not in all studies (Tatemichi et al., 1990; Pohjasvaara et al., 1998). However, some reports indicate that there is an association between AF and dementia even without stroke (Ott et al., 1997; Kilander et al., 1998a; Sabatini et al., 2000; Tilvis et al., 2004; Elias et al., 2006). These controversial results may be related to the cohort differences and different definitions for AF and cognitive decline used in the various studies. The neuropathological study strongly indicates that AF contributes mainly to macroscopic infarcts but not to the brain pathology that associates with dementia with AD-type pathology and small infarcts.

The probability for developing dementia during the follow-up was higher for those who had DM at the baseline. The association with DM and cognitive decline in old people has been reported earlier (Hassing et al., 2004). DM may contribute to the risk of dementia mainly through vascular pathology and thus the development of incident dementia in those subjects with DM could be due to accelerated vascular brain disease. However, DM has been associated both with VaD (O´Leary et al., 1992; Mast et al., 1995; Hassing et al., 2002; MacKnight et al., 2002; Peila et al., 2002; Xu et al., 2004) and AD (Leibson et al., 1997; Brayne et al., 1998; Ott et al., 1999). The mechanisms behind the association remain unclear and it should be recalled that many studies have shown no association with DM and AD (Yoshitake et al., 1995; Luchsinger et al., 2001; Hassing et al., 2002; MacKnight et al., 2002; Piguet et al., 2003; Xu et al., 2004; van den Berg et al., 2006).

In contrast to the studies showing the association between high midlife BP and later dementia, a previously diagnosed hypertension seemed to be protective against the development of incident dementia during the follow-up in this very old population. Many crosssectional and longitudinal studies have revealed either the association between high BP and cognitive decline (Starr et al., 1993; Cacciatore et al., 1997; Haan et al., 1999; Harrington et al., 2000; Budge et al., 2002; Elias et al., 2003; Piguet et al., 2003; Kuo et al., 2004; Waldstein et al., 2005; Reitz et al., 2007) or conversely low BP and cognitive decline or dementia (Guo et al., 1996; Rockwood et al., 1996; Guo et al., 1997a,b; Morris et al., 2000; Pandav et al., 2003; Kähönen-Väre et al., 2004). Many studies have reported no association or a U-shaped association between BP and dementia (Farmer et al., 1987; Scherr et al., 1991; Ueda et al., 1992; Guo et al., 1997a,b; Kuusisto et al., 1997; Glynn et al., 1999; Cervilla et al., 2000; Bohannon et al., 2002; Hebert et al., 2004; Solfrizzi et al., 2004; Tervo et al., 2004; Waldstein et al., 2005; Shah et al., 2006; Raffaitin et al., 2009). The contribution of BP to cognition in old age has thus remained unclear and more studies have been waited for in this very special population which differs clearly from younger people. On one hand, hypertension is associated with atherosclerosis and that can cause vascular cognitive impairment or even AD (Qiu et al., 2005, Birns et al., 2006), on the other hand, low BP can cause hypoperfusion of the brain (Lithell et al., 2003). More light on this matter was shed in a recent, large treatment trial, Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG) in which cognitive function was assessed in relatively well-functioning subjects aged 80 years and over during a 2.2-year follow-up. After combined results in a meta-analysis with other placebo-controlled trials of antihypertensive treatment, a significant reduction of incident dementia was observed in treatment group compared to non-treatment group (Peters et al., 2008).

6.5. Brain pathology contributing cognitive decline in the very old

The results showed that different pathological changes in the brain contributed to cognitive decline. β-amyloid load and vascular changes, particularly a high number of small infarcts or subcortical vascular pathology were associated with dementia. The

results support the hypothesis that the neuropathological background for dementia is complex in the very old. Neuritic plaques and neurofibrillary tangles, mainly in the neocortex, the entorhinal cortex, and the hippocampus are the hallmark neuropathological changes encountered in AD (Braak and Braak, 1995; Haroutunian et al., 1998; Morris and Price, 2001). However, the influence of NFTs and neuritic plaques on the severity of dementia seems to disappear in the very old (Prohovnik et al., 2006) and these typical AD related neuropathological changes have also been found in brains of cognitively intact subjects (Braak and Braak, 1995; Haroutunian et al., 1998; Haroutunian et al., 1999, Davis et al., 1999; Schmitt et al., 2000; Morris and Price, 2001; Knopman et al., 2003; Bennet et al., 2006; Haroutunian et al., 2008). Several studies have also shown that dementia may develop in the oldest old in the absence of clear neuropathological sequelae and conversely a significant proportion of very old demented subjects do not meet the pathological criteria for AD (Crystal et al., 2000; Xuereb et al., 2000; Jellinger, 2001; Silver et al., 2002; Haroutunian et al., 2008). The recent neuropathological study found that the cinical manifestation of dementia and underlying neuropathological findings varies with age. They found that the association between neocortical neuritic plaques and dementia was strong at 75 years of age and reduced at 95 years of age. However, neocortical cerebral atrophy maintained a relationship with age (Savva et al., 2009).

The importance of microvascular pathological correlates and small vessel disease in development of cognitive decline has been shown previously, and the number, volume and location of vascular lesions have been associated with the severity of the cognitive decline (Tomlison et al., 1970; del Ser et al., 1990; Fein et al., 2000; Kövari et al., 2004; Gold et al., 2005; Imhof et al., 2007; Tomimoto et al., 2007). Also the precence of severe age related white matter changes predict more rapid decline in global functioning independently of baseline cerebral atrophy or strokes (Inzitari et al., 2009).

Both AD and VaD may exist also simultaneously (Sadowski et al., 2004; Jellinger 2007; Schneider et al., 2007) and at least 30% of AD subjects display evidence of cerebral infarction (Olichney et al., 1997). Large vessel cerebrovascular disease or Lewy body disease may also contribute to the cognitive decline (Snowden et al., 1995; Giannakopoulous et al., 2007).

Our results showed that mixed brain pathologies for dementia in the very old population may play a significant role in cognitive decline. This is in line with the previous studies (Xuereb et al., 2000; Schneider et al., 2007; MRC CFAS, 2001).

7. SUMMARY AND CONCLUSIONS

Vascular risk factors are important risk factors for dementia and stroke. They are linked not only with VaD but also with AD. The nature of AD seems to resemble more a syndrome with multiple risk factors. However, the risk factors present in midlife may be different from those in the very old. Moreover, mixed brain pathologies that contribute to the cognitive decline leading to the dementia syndrome in the very old with both degenerative changes and vascular pathology seem to be important.

1) APOE did not associate with BP, AF, or other cardiac arrhythmias, but APOE ε4 associated with high levels of total cholesterol and LDL-cholesterol.

2) Low SBP (<140 mmHg) associated with mortality and this association was most obvious in subjects without dementia, cancer, or stroke. The association was seen in both sexes.

3) Chronic AF associated with stroke as well as with macroscopical brain infarcts, particularly with multiple large lesions. However, it was not associated with dementia or AD pathology in the brain.

4) Clinical stroke showed a strong association with dementia. DM, low education, and a new incident stroke predicted incident dementia during the follow-up. A previous diagnose of hypertension was associated with incident dementia negatively.

5) The neuropathological correlates for dementia were amyloid load and multiple small infarcts.

In conclusion, the role of APOE genotype and some other vascular risk factors may weaken with age. The influence of these risk factors on dementia in this age-group is probably mainly mediated through cerebrovascular morbidity as indicated by the strong association between stroke and dementia. The very old are extremely susceptible to

cerebrovascular disease and this may affect the results. The very old are not comparable with younger people with respect to vascular risk factors or causalities with dementia or mortality. However, it appears that prevention of stroke and DM may reduce the prevalence of cognitive decline in very old individuals. Since AF is a major risk factor for stroke in this very old population the treatment of AF is extremely important. Effective prevention still remains the best treatment for reducing the burden of stroke and primary prevention of stroke is particularly important also to remain the cognitive reserve. Although hypertension is well established risk factor of stroke, the effects of BP are controversial in epidemiological studies in very old people, possibly because lower and higher BPs are indicators of reduced and maintained reserves, respectively. The present results do not rule out the possibility that treatment of hypertension is of a value also in oldest patients, but their treatment must be individually assessed.

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APPENDIX:
ORIGINAL PUBLICATIONS (I-IV)

I

Association of apolipoprotein E genotypes, blood pressure, blood lipids and ECG abnormalities in general population aged 85+.

Sari Rastas, Kimmo Mattila, Auli Verkkoniemi, Leena Niinistö, Kati Juva, Raimo Sulkava, Esko Länsimies.

BMC Geriatr 2004;29:4:1.

II

Association between Blood Pressure and Survival over Nine Years in a General Population Aged 85 Years and Over.

Sari Rastas, Tuula Pirttilä, Petteri Viramo, Auli Verkkoniemi, Pirjo Halonen, Kati Juva, Leena Niinistö, Kimmo Mattila, Esko Länsimies, Raimo Sulkava.

J Am Geriatr Soc 2006;54:912-918.

IIb

Response letter to Dr Cheng.

Sari Rastas, Tuula Pirttilä, Petteri Viramo, Auli Verkkoniemi, Pirjo Halonen, Kati Juva, Leena Niinistö, Kimmo Mattila, Esko Länsimies, Raimo Sulkava.

J Am Geriatr Soc 2007; 55:137.

III

Atrial Fibrillation, Stroke and Cognition: A Longitudinal Population Based Study of People Aged 85+.

Sari Rastas, Auli Verkkoniemi, Tuomo Polvikoski, Kati Juva, Leena Niinistö, Kimmo Mattila, Esko Länsimies, Tuula Pirttilä, and Raimo Sulkava.

Stroke 2007;38:1454-1460.

IV

Vascular risk factors and dementia in the general population aged 85+. Prospective population-based study.

Sari Rastas, Tuula Pirttilä, Kimmo Mattila, Auli Verkkoniemi, Kati Juva, Leena Niinistö, Esko Länsimies, Raimo Sulkava.

Neurobiol Aging 2008 Mar 29.

SERIES OF REPORTS, DEPARTMENT OF NEUROLOGY

1. **Juhani Partanen (1978):** Time-locked phenomena of human motor unit potentials. An electromyographic study of satellites and doubles.
2. **Eeva Leino (1981):** Clinical and biochemical studies on progressive myoclonus epilepsy.
3. **Hilkka Soininen (1981):** Senile dementia. A clinical, neurochemical and etiological study.
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5. **Markku Saksa (1982):** The autonomic nervous system in experimental allergic neuritis. A functional, morphological and biochemical study.
6. **Juhani Sivenius (1982):** Studies on the rehabilitation, epidemiology and clinical features of stroke in East Central Finland.
7. **Asla Pitkänen (1987):** Somatostatin in epilepsy. An experimental and clinical study.
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