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132

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THE THIRD STROKE REGISTRY IN TARTU, ESTONIA FROM 2001 TO 2003: INCIDENCE, CASE-FATALITY, RISK FACTORS AND LONG-TERM OUTCOME

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Commencement: May, 2nd 2007. Biomedicum, Tartu

Publication of this dissertation is granted by the University of Tartu

ISSN 1024–395X
ISBN 978–9949–11–574–7 (trükis)
ISBN 978–9949–11–575–4 (PDF)

Tartu Ülikooli Kirjastus
www.tyk.ee
Tellimus nr 134

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

I Vibo R, Kõrv J, Haldre S, Roose M. First Year Results of the Third Stroke Registry in Tartu, Estonia. Cerebrovascular Diseases 2004; 18:227–231.

II Vibo R, Kõrv J, Roose M. The Third Stroke Registry in Tartu, Estonia from 2001 to 2003. Acta Neurologica Scandinavica 2007; DOI 10.1111/j.1600-0404, 2006.00710x Published online on 5th February, 2007. In press.

III Vibo R, Kõrv J, Roose M. The Third Stroke Registry in Tartu, Estonia: decline of stroke incidence and 28-day case-fatality rate since 1991. Stroke 2005; 36:2544–2548.

IV Vibo R, Kõrv J, Roose M. Insuldi haigestumusuuringud Tartus: 30 aasta kogemus. Eesti Arst 2006; 85:665–670.

V Vibo R, Kõrv J, Roose M. One-year outcome after first-ever stroke according to stroke subtype, severity, risk factors and pre-stroke treatment. A population-based study from Tartu, Estonia. European Journal of Neurology 2007; 14:435–439.

VI Vibo R, Kõrv J, Roose M, Kampus P, Muda P, Zilmer K, Zilmer M. Acute phase proteins and oxidised low-density lipoprotein in association with ischemic stroke subtype, severity and outcome. Free Radical Research 2007; 41:282–287.

ABBREVIATIONS

ADL	activities of daily living
AF	atrial fibrillation
ASIR	age-standardised incidence rate
BI	Barthel Index
CE	cardioembolism
CFR	case-fatality rate
hsCRP	high-sensitive C- reactive protein
CT	computerised tomography
DNN	Department of Neurology and Neurosurgery
EU	European Union
EUR	European standard population
Hcy	homocysteine
HDL	high density lipoprotein
hHcy	hyperhomocysteinaemia
ICH	intracerebral haemorrhage
IS	ischemic stroke
LAA	large-artery atherosclerosis
LDL	low density lipoprotein
MONICA	Monitoring Trends and Determinants in Cardiovascular Disease
mRS	modified Rankin Scale
NC	not classified type of stroke
OC	stroke due to other determined causes
OR	odds ratio
oxLDL	oxidised low density lipoprotein
SAH	subarachnoid haemorrhage
SAO	small-vessel occlusion
SD	standard deviation
SSS	Scandinavian Stroke Scale
SSS0	Scandinavian Stroke Scale on admission
SSS7	Scandinavian Stroke Scale on the 7^{th} day following stroke
TIA	transient ischemic attack
UND	stroke due to an undetermined cause
WHO	World Health Organisation

INTRODUCTION

Stroke incidence, time trends and geographical variations have already been in the centre of interest for several years. The possibilities to reduce stroke related morbidity and mortality are constantly looked for. Some questions have been answered and progress in primary and secondary prevention has been made, but the incidence of stroke remains high, especially in Eastern Europe.

Although many stroke risk factors have already been known for years, scientists all over the world are trying to find possible new and treatable risk factors and treatment options for stroke to minimise the burden of stroke in the community.

Population-based stroke registries are the most important sources in providing information about stroke epidemiology in different geographical regions. Stroke registries are the only reliable sources allowing the evaluation of the efficiency of local health promotion programmes, the influence of newly introduced treatment and management strategies on the incidence and case-fatality of stroke and also to determine the overall burden of stroke in a population.

There is a long history of stroke epidemiology in Tartu, Estonia. The stroke registeries, on a regular basis, give a unique possibility to assess stroke trends in the same population over several decades. In addition, the compatibility of the study designs enables the comparison of results with other populations.

During the 1990s, Estonia has changed from a former Soviet Union republic to an independent country in the European Union. Such remarkable changes in a community may cause stress, change lifestyle and affect the health of population. At the beginning of the 1990s, reorganisation of the health care system and implementation of evidence-based medicine commenced in Estonia. Regular population-based studies enable the evaluation of whether such changes also influence stroke incidence, case-fatality and/or outcome in a well-defined population.

REVIEW OF THE LITERATURE

1. Incidence and case-fatality of stroke

1.1. The study design issues

The incidence of a disease is the frequency of new disease occurrences within a defined time interval in a defined population. It is very easy to draw incidence data from official health statistics of some countries, but it hardly expresses the true situation in the community (*Thorvaldsen et al. 1997*) and therefore the use of population-based registries is preferred. Many studies, estimating the incidence of stroke in the community, have been conducted worldwide. However, to be comparable, all studies must use the same definitions, methods and mode of data presentation. A well-conducted study can be relatively useless if the certain standard criteria are not followed.

The first attempt to establish standardised criteria for stroke incidence studies, was the WHO MONICA study at the beginning of the 1980s (*Sudlow and Warlow 1996, Thorvaldsen et al. 1997*). This large international study comprised 17 populations from 10 countries and analysed trends in the incidence of myocardial infarction and stroke in subjects aged 25–64 years. The uniform data collection and analysis methods provided a good possibility to compare stroke incidence in different countries and to observe temporal changes in incidence with time. However, the limited age-group involvement prohibits the comparison of these results with those obtained from population-based studies.

In 1987, Malmgren and colleagues reviewed studies of stroke incidence from around the world and found that only 9 studies out of 65 met a set of standard criteria sufficiently to be considered comparable with each other (*Malmgren et al. 1987*). In 1996, Sudlow and Warlow published an article which aimed to extend and refine the original Malmgren criteria (*Sudlow and Warlow 1996*). Their suggestions were not based only on an extensive review of the literature but also on a series of visits around the world to meet with investigators in centres where stroke incidence has been studied. The most important criteria for a comparable study of stroke incidence are summarised in Table 1.

Table 1. Core criteria for a stroke incidence study (adapted from Sudlow and Warlow (*1996*))

Standard definitions WHO definition First-ever-in-a-lifetime stroke
Standard methods Complete, community-based case ascertainment, based on multiple overlapping sources Prospective study design Large, well-defined, stable population Reliable method for estimating denominator
Standard data presentation Whole years of data Not >5 years of data averaged together Men and women presented separately Include cases ≥85 years if possible Standard mid-decade age bands (e.g., 55–64 years) used in publications Unpublished 5-year age bands available for comparison with other studies Presentation of 95% confidence intervals around incidence rates

Although those criteria are widely propagated, many authors still do not follow them in designing the studies and presenting the results. Some papers still do not provide standardised data and thus, are not comparable with results from others.

1.2. Stroke incidence studies before 1990

The first stroke incidence studies had already been conducted in the 1940s (*Dalsgaard-Nielsen 1955, Whisnant et al. 1971*). Many of these studies, at that time, were cohort (*Heyman et al. 1971*) or retrospective (*Brewis et al. 1966, Alter et al. 1970, Whisnant et al. 1971*) studies. Still, several prospective studies were also conducted (*Eisenberg et al. 1964, Parrish et al. 1966, Acheson et al. 1968, Wallace 1971, Harmsen and Tibblin 1972*). Unfortunately, several of those also included TIA (*Alter et al. 1970, Acheson et al. 1968*) or were hospital-based (*Acherson and Fairbairn 1970, Melamed et al. 1973*). The incidence varied from 66/100 000 in Denmark (*Dalsgaard-Nielsen 1955*) to 764/100 000 in Great Britain (*Acheson et al. 1968*). The CFR was 35 to 61% (*Eisenberg et al. 1964, Parrish et al. 1966, Wallace 1971, Whisnant et al. 1971, Harmsen and Tibblin 1972*). However, the study criteria were not identical across studies.

Most of the stroke incidence studies in the 1980s represent the results from the large international MONICA project (*Thorvaldsen et al. 1997*) which

included patients aged 25 to 64 years. Other studies were conducted in Oxfordshire, England (*Bamford et al. 1988, Bamford et al. 1990*), Söderhamn, Sweden (*Terent 2003*) Novosibirsk, Russia (*Feigin et al. 1995*) and in Rochester, USA (*Brown et al. 1996*). Novosibirsk and two Swedish cities (*Thorvaldsen et al. 1997*) were also MONICA populations, but the other studies mentioned were conducted involving all age bands.

The WHO MONICA project showed the lowest stroke incidence rates in Italy and the highest in Russia. Relatively low incidence rates were also found in Swedish, German and Danish populations (*Eisenblätter et al. 1995*, *Stegmayr et al. 1996, Thorvaldsen et al. 1997*). China, Lithuania, Finland and Russia revealed higher rates (*Tuomilehto et al. 1992, Cheng et al. 1995, Feigin et al. 1995, Rastenyte et al. 1995*, *Stegmayr et al. 1996, Thorvaldsen et al. 1997*). Stroke incidence rates varied threefold among men and fivefold among women in these populations (*Thorvaldsen et al. 1997*).

The 28-day CFR varied from 14% in Sweden to 33% in Russia (*Thorvaldsen et al. 1997*).

Because MONICA populations were studied for 5 to 6 years, it was also possible to determine the time trends of stroke incidence. The decline in stroke incidence rate was evident in most of the populations studied and it reached statistical significance among men in two and among women in three populations (*Thorvaldsen et al. 1997*). The MONICA project also revealed that the incidence of stroke can be substantially different in various populations of the same country (*Thorvaldsen et al. 1997*) and this has also been shown by some other studies (*Feigin et al. 1996*).

1.3. Stroke incidence studies beyond 1990

During the 1990s, several well designed stroke incidence studies were published (*Kõrv et al. 1996, Carolei et al. 1997*, *Ellekjær et al. 1997, Kõrv et al. 1997*, *Kolominsky-Rabas et al. 1998*, *Vemmos et al. 1999*, *Johansson et al. 2000, Wolfe et al. 2000*, *Mihálka et al. 2001*, *DiCarlo et al. 2003*). Most of them are listed in Table 2. The requirements of an „ideal" epidemiology study were considerably better followed compared to previous reports. This allows also better comparability between these studies.

The crude incidence rate of stroke in the 1990s varied in different centres from 130 to 344/100 000 (*Vemmos et al. 1999, Wolfe et al. 2000*). Incidence rate, standardised to the European standard population, was lowest in France (*Wolfe et al. 2000*) and highest in Ukraine (*Mihálka et al. 2001*). The incidence of stroke has always been somewhat higher in Eastern Europe compared to Western countries (*Asplund 1996, Stegmayr et al. 2000*). Nevertheless, the rate from Greece (Arcadia registry) was relatively high and the rate in Estonia (*Kõrv et al. 1997*) was only modest compared to other centres. Furthermore, a recent

study from Georgia (Tbilisi) reported low crude and standardised incidence rates (165 and 150/100 000, respectively) (*Tsiskaridze et al. 2004*).

The standardised incidence rate of stroke is highly correlated with the proportion of older people in the community and this figure in Europe varies from 10 to 25% (*Marini et al. 2001*). Therefore, it is important to consider the proportion of elderly residents in the community when interpreting the stroke incidence rates.

Table 2. Age-specific incidence rates per 100 000 in stroke epidemiology studies in Europe during the 1990s

	Crude incidence rate	**ASIR***
Arcadia, Greece, 1993–95 (*Vemmos et al. 1999*)	344	319
Lund-Orup, Sweden, 1993–95 (*Johansson et al. 2000*)	194	158
Inherred, Norway, 1994–96 (*Ellekjær et al. 1997*)	312	221
L'Aquila Italy, 1994–98 (*Carolei et al. 1997*)	275	228
Vibo-Valencia, Italy, 1996 (*DiCarlo et al. 2003*)	199	136
Erlangen, Germany, 1995–97 (*Kolominsky-Rabas et al. 1998*)	174	134
London, England, 1995–97 (*Wolfe et al. 2000*)	130	124
Uzhgorod, Ukraine, 1999–00 (*Mihálka et al. 2001*)	281	341
Dijon, France, 1995–97 (*Wolfe et al. 2000*)	138	100
Tartu, Estonia, 1991–93 (*Kõrv et al. 1997*)	250	230

* Standardised to EUR

When comparing the incidence in age-groups among men, the highest rates were found in Ukraine, except for those aged ≥85 years. No cases were registered in this group in the Ukrainian registry. This fact raises a question of the completeness of the registry. Either, the life-expectancy in Ukrainian men is so low that the residents do not live to an advanced age or some cases from the oldest age-group have been missed. It is however known, that the official mortality rate for cardiovascular disease of the EU average is 220/100 000, but 780/100 000 in Ukraine (*WHO 2002*).

The lowest 28-day CFR were registered in France (*Wolf et al. 2000*), Norway (*Ellekjær et al. 1997*) and Germany (*Kolominsky-Rabas et al. 1998*), 13%, 18% and 19%, respectively. Somewhat higher rates were detected in Estonia (*Kõrv et al. 1997*), Italy (*Carolei et al. 1997*), Greece (*Vemmos et al. 1999*), England (*Wolf et al. 2000*), Ukraine (*Mihálka et al. 2001*), Denmark (*Truelsen et al. 2002*) and Georgia (*Tsiskaridze et al. 2004*).

While Ukraine (*Mihálka et al. 2001*) had the highest incidence rate (341/100 000), the 28-day CFR was relatively low (23%). This also supports the assumption, that some cases from the oldest age-groups and/or non-hospitalised

cases were possibly missed. On the contrary, low stroke incidence in England (*Wolf et al. 2000*) was accompanied by high 28-day CFR (27%).

When the CFR of different stroke subtypes are analysed, the highest rates are usually found for haemorrhagic stroke subtypes (usually between 35 to 50%), while the rates for IS are between 10 to 22% (*Carolei et al. 1997*, *Ellekjær et al. 1997*, *Kõrv et al. 1997*, *Kolominsky-Rabas et al. 1998*, *Vemmos et al. 1999*, *DiCarlo et al. 2003*). The CFR for NC stroke varies remarkably and this phenomenon is probably related to different study criteria and availability of CT scans for the diagnosis of stroke. Germany (*Kolominsky-Rabas et al. 1998*), Italy (*DiCarlo et al. 2003*) and Georgia (*Tsiskaridze et al. 2004*) have reported the highest CFR for NC strokes – 69%, 62% and 70%, respectively.

Unfortunately, only a few papers provide information about age- and sex-specific CFR (*Kõrv et al. 1997, Vemmos et al. 1999*, *Mihálka et al. 2001*). From these data it can be seen, that the case-fatality in younger age-groups is comparable and major differences are seen in older ages (see Table 3). This could be related to the quality and completeness of case-ascertainment methods used, but also to the post-stroke care and rehabilitation facilities.

Table 3. Age-specific 28-day CFR of stroke patients from selected studies

Age-group	Arcadia, Greece 1993–95	Uzhgorod, Ukraine 1999–00	Tartu, Estonia 1991–93
0–44		8	6
45–54	19*	18	21
55–64	14	19	17
65–74	22	24	25
75–84	27	34	40
≥85	38	80	52
Total	27	23	30

* Age group 18 to 54 years

1.4. Stroke epidemiology in Estonia

Two previous studies on stroke epidemiology have been conducted in Estonia. Both studies were carried out in Tartu.

The first study was conducted from 1970 to 1973 (*Roose 1977*). A total of 667 first-ever stroke cases, among the population of 90 459 (1970 census) were registered. The crude incidence rate of first ever stroke was 184/100 000 (*Zupping and Roose 1976*) and it was close to the rates reported by other studies carried out in several communities before the 1970s. In most age-groups (except for that of 80 to 89 years) the rates for IS were higher for men and the total age-

and sex-adjusted rate was also higher for men (*Roose 1977*). The same trend was shown for ICH. However, the CFR at 30 days (49%) was higher than shown by others, especially for IS and ICH (*Roose 1977*). This was explained by the higher mean age of the population of Tartu and lower admission percentage of the stroke patients in the acute stage.

The second stroke epidemiology study was carried out in Tartu from 1991 through 1993 (*Kõrv 1998*). During the study period of three years, 829 first-ever stroke cases were registered among a population of 110 631 (mean population from 1991 to 1993) (*Kõrv et al. 1996*). The crude incidence rate was 250/100 000 which was significantly higher compared to the previous study (*Zupping and Roose 1976*). In most age-groups, the rates for men were higher than those for women, but the rates for women aged 75 to 84 years were higher (*Kõrv 1998*). The 30-day CFR had declined to 30% It was speculated, that the rate could have declined due to the changes in the natural history of stroke, better management of stroke in the acute phase and the higher rate of hospitalisation during the second period (34 vs. 72%) (*Kõrv 1998*).

Different age-group stratification was used during the first study period and thus the comparison of data is somewhat restricted. Both studies have used the same data finding methods, only the partial availability of a CT scan during the second study period (CT was not used during the first period) might have influenced the diagnosis and subtyping of stroke (*Kõrv 1998*).

1.5. The incidence of TIA

The incidence of TIA in a community is difficult to measure. As TIA leaves no persistent neurological deficit and often subsides quickly, many patients do not seek medical help at all. Many TIA patients refer only to their general practitioner (often days or weeks after the event). Moreover, a TIA is often hard to diagnose, because the symptoms are not always typical (*Bots et al. 1997*). TIA is a warning sign for the development of ischemic stroke and those patients should be managed with extreme care to prevent a future stroke.

The incidence of TIA should be determined using population-based registries and standardisation of rates (to European and/or world population). There are only a few studies assessing the incidence of TIA using a population-based design (*Whisnant et al. 1973, Roose 1977, Dennis et al. 1989, Ricci et al. 1991, Kõrv 1998, Rothwell et al. 2004a, Kleindorfer et al. 2005, Correia et al. 2006, Bejot et al. 2007*). The crude incidence rates of TIA in selected populations are presented in Table 4.

Table 4. Crude incidence rates of TIA (per 100 000) in selected populations

Study centre	Men	Women	Total
Rochester 1955–69 (*Whisnant et al. 1973*)	31	31	31
Tartu 1970–73 (*Roose 1977*)	25	39	33
Oxfordshire 1981–86 (*Dennis et al. 1989*)	39	31	35
Umbria 1986–91 (*Ricci et al. 1991*)	63	65	64
Tartu 1991–93 (*Kõrv 1998*)	24	32	28
Cincinnati 1993–94 (*Kleindorfer et al. 2005*)	101	67	83
Dijon 1985–04 (*Bejot et al. 2007*)	19	25	22
Northern Portugal 1998–00 (*Correia et al. 2006*)	66	69	67
Oxfordshire 2000–04 (*Rothwell et al. 2004a*)	35	69	51

However, the comparison of these data is restricted, because studies have used different standard populations and methods for data collection. For example, the Cincinnati study (*Kleindorfer et al. 2005*) has included both first-ever and recurrent TIA and therefore the rates are naturally higher compared to others. The mean age of TIA patients varies from 64 (*Roose 1977*) to 73 years (*Bejot et al. 2007*).

The incidence of TIA in Tartu has been quite stable over the past 20 years (*Roose 1977, Kõrv 1998*). The mean age of patients is the lowest compared to other populations and could be associated with the overall shorter life-expectancy in Eastern-European countries.

1.6. Trends in stroke incidence and 28-day case-fatality

Several studies concerning stroke time trends have been published (*McGovern et al. 1993*, *Eisenblätter et al. 1995*, *Brown et al. 1996*, *Kõrv et al. 1996, Liu et al. 2001*, *Cayuela et al. 2002*, *Truelsen et al. 2002*, *Immonen-Räihä et al. 2003*, *Pessah-Rasmussen et al. 2003*, *Rothwell et al. 2004a, Pajunen et al. 2005, Benatru et al. 2006*). The design of these studies differ remarkably – registry-based (*Eisenblätter et al. 1995*, *Brown et al. 1996*, *Kõrv et al. 1996, Immonen-Räihä et al. 2003*, *Rothwell et al. 2004a, Benatru et al. 2006*), hospital-based (*McGovern et al. 1993*), using data from official statistics (*Liu et al. 2001*, *Cayuela et al. 2002*, *Truelsen et al. 2002*, *Pajunen et al. 2005*) or involving cases from limited age-groups (*McGovern et al. 1993*, *Eisenblätter et al. 1995*, *Liu et al. 2001*, *Pessah-Rasmussen et al. 2003*). All these results are valuable, but can not be extrapolated to the whole population at risk, and the described differences in mortality and incidence between different regions may be mistaken because of methodological biases.

The results, from studies considering stroke time trends, have been conflicting. Mostly, the decline in stroke mortality is reported (*Liu et al. 2001*,

Cayuela et al. 2002, *Truelsen et al. 2002*, *Immonen-Räihä et al. 2003*, *Pessah-Rasmussen et al. 2003*, *Rothwell et al. 2004a, Pajunen et al. 2005*) and some centres show a trend of increasing stroke incidence (*Eisenblätter et al. 1995*, *Pessah-Rasmussen et al. 2003*). In the Copenhagen City Heart Study stroke case-fatality did not change over a 15-year period, but the 1-year survival improved in 28-day survivors (*Truelsen et al. 2002*). No change in CFR was also detected in Rochester, Minnesota (*Brown et al. 1996*) and in Cincinnati, Ohio (*Kleindorfer et al. 2006*). A 10-year stroke registry in Malmö, Sweden reported a significant decline in 28-day CFR for women but the rate for men did not change (*Pessah-Rasmussen et al. 2003*). The FINSTROKE registry from Finland showed a significant decline in case-fatality for both sexes during the 15-year study period (*Sivenius et al. 2004*), similar results were reported from Dijon, France (*Benatru et al. 2006*).

Several stroke time trend studies have shown that improvements in primary prevention have a significantly higher impact on the incidence of stroke compared to case-fatality. CFR is more dependent on the acute care of stroke. However, the severity of stroke might be related to the extent and quality of primary prevention and therefore a slight decline in CFR can also be seen in some populations over time due to the improvements in primary prevention strategies. Increasing incidence has been linked to the implement of CT in the 1980s through the 1990s (i.e., increased detection of milder strokes) and also to the detected unfavourable changes in risk factor profiles in certain communities (*Eisenblätter et al. 1995*).

2. Mortality of stroke

The last decades of the 20th century were marked by an increasing east-west gradient in mortality and an increasing gap in life expectancy between people living in the eastern and western parts of the European region (*WHO 2002*). Stroke is the third common cause of death in developed countries, exceeded only by coronary heart disease and cancer. In Estonia, about 2900 people die from stroke every year (*Mackay and Mensah 2002*). The 28-day CFR characterises the early outcome of stroke, but the term “mortality” is used to define the number of deaths per 100 000 population . A majority of official health statistics are based on mortality data which can easily be collected. However, in contrast to stroke registries, the accuracy of the diagnosis or the cause of death can not be evaluated. Nevertheless, official mortality data provide a useful source of information about the epidemiology of a disease and allow comparisons of different populations.

Liu et al. have analysed the mortality of stroke (population aged 55 to 79 years) in Japan over a 47-year period (*Liu et al. 2001*). They reported a continuous decline in stroke mortality over time; the decline was more evident

among women. A similarly designed Spanish study also reported a decline in stroke mortality (population aged ≥35 years) over a 17-year period (*Cayuela et al. 2002*). The estimated mean decline was 3.4% per year both for men and for women. A 10-year stroke mortality data analysis for Finland revealed a decrease in the mortality rates of all subtypes of stroke in both sexes in patients aged 35 to 74 years. Among patients 75 years and older, the mortality of IS also declined (*Pajunen et al. 2005*). A recent study from Brazil shows progressive decline in stroke mortality from 1980 to 2002, for both men and women (*André et al. 2006*).

The standardised mortality rate of cardiovascular diseases in Estonia is comparable to other European countries, but the rate for ischemic heart disease holds second place in the region (age standardised mortality rate 76.4/100 000) (*WHO 2001*). The age-standardised mortality rate for cerebrovascular diseases (36.3/100 000) in Estonia has declined and is about the EU average (32.6/100 000) (*WHO 2001*).

3. Risk factors for stroke

Although therapies to reduce brain injury from acute stroke are being developed, prevention by treating stroke risk factors continues to be the most effective strategy for reducing the health consequences and cost of stroke.

Hypertension. The Estonian Elderly Subjects Managing and Health Survey in 2000 showed that 61% of elderly subjects (age ≥65 years) have hypertension (*Saks et al. 2000*). Similar results have also been found in other populations (*Hadijev et al. 2003*). The prevalence of hypertension among younger age-groups has been also studied in Estonia (*Abina et al. 2003*). The results show that 41% of men and 23% of women aged 40–49 years, and 61% of men and 41% of women aged 50–54 years have hypertension.

Hypertension is the most important modifiable risk factor both for ischemic and hemorrhagic stroke, the use of antihypertensive treatment reduces the risk of stroke by about 40% (*WHO 2003*, *Lawes et al. 2004*). Treating all hypertensive patients would reduce the mortality of stroke by 15% (*Humphrey et al. 1994*). Current WHO guidelines define hypertension as systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg. The risk of cardiovascular disease doubles for every 10 point increase in diastolic blood pressure or every 20 point increase in systolic blood pressure regardless of age (*Lawes et al. 2004*, *Rodgers et al. 2004*). Several trials have also shown that high risk hypertensive patients benefit from higher blood pressure reductions and the target pressure for those individuals should be <130/80 mmHg (*WHO 2003*).

The prevalence of hypertension among stroke patients is usually somewhat higher. In the WHO MONICA project, the prevalence of hypertension was from

10 to 42%, but this study included only patients aged 35–64 years (*Stegmayr et al. 1997*). The MONICA population analysis found no significant correlation between the stroke incidence rate and risk factors, but in women the variation in risk factor prevalence explained 42% of the variations in stroke incidence rate (*Stegmayr et al. 1997*). A population-based stroke registry from Arcadia (Greece) reported 81% of patients with hypertension (*Vemmos et al. 1999*) and 85% of patients had hypertension in Novosibirsk (Russia) (*Feigin et al. 1998*). In the previous stroke registry in Tartu 1991–93 the prevalence of hypertension was 50%, but the cut-off point for the diagnosis of hypertension was higher (≥165/95 mmHg) at that time (*Kõrv et al. 1997*) compared to currently valid guidelines.

Diabetes. Diabetes constitutes a risk factor for chronic heart disease, hypertension and stroke (*Chukwuma and Tuomilehto 1993*, *Lukovits et al. 1999*). Diabetes augments the risk of stroke by the promotion of cerebroatherogenesis and triggering of other major risk factors. For example, in hypertensive patients diabetes increases the risk of stroke two to three times. On the other hand, also in the absence of diabetes, hyperglycaemia, due to a stress response following stroke, can occur. The resultant effect is increased catecholamine release, augmented lipolysis with concomitant increased levels of free fatty acids constitute a marker of poor prognosis (*Chukwuma and Tuomilehto 1993*, *Capes et al. 2001*). It was recently shown that mean blood glucose levels rather than blood glucose value on admission or glycosylated haemoglobin play an important role determining the outcome of stroke (*Farrokhina et al. 2005*).

The incidence of atherothrombotic cerebral infarction in diabetic individuals is higher compared to non-diabetic patients (*Chukwuma and Tuomilehto 1993*, *Mankovsky et al. 1996*, *Lukovits et al. 1999*). Moreover, diabetic stroke patients have a higher case-fatality, worse neurological outcome and more severe disability than those without diabetes. Several studies have shown a worse outcome of diabetic patients following stroke, both in a short and long-term basis (*Mankovsky et al. 1996*, *Capes et al. 2001, Farrokhina et al. 2005*).

Several prospective studies have evaluated the risk of stroke in diabetic patients (*Lukovits et al. 1999*), the relative risk of stroke in these populations varies from 1.7 to 5.8 (*Stegmayr and Asplund 1995, Lukovits et al. 1999*). The prevalence of diabetes among stroke patients has geographical variations and ranges from 7 to 21% (Jørgensen *et al. 1994a*, *Stegmayr and Asplund. 1995*, *Kõrv et al. 1997, Feigin et al. 1998*, *Rodgers et al. 2004*).

Atrial fibrillation. Atrial fibrillation is a common cardiac arrhythmia among elderly and a risk factor for stroke. The prevalence of AF in the general population is about 1%, but as much as 6% among subjects aged >65 years and >10% in subjects aged >75 years (Jørgensen *et al. 1996a, Donnan et al. 2004*). The risk of stroke in patients with AF is 3 to 5%/year overall and 12 to 15%/year in high-risk patients with additional risk factors (*Donnan et al. 2004,*

Leys et al. 2004). AF reduces cardiac output and the resulting ineffective atrial contraction increases the risk of intra-atrial clot formation and subsequent thrombembolic events.

The Copenhagen Stroke Study clearly showed that patients with AF have more severe strokes and as a consequence the mortality rate is increased by 70%, a relative chance of discharge to home is decreased by 40% and the stroke survivors with AF have significantly higher impairment and disability prevalence (Jørgensen *et al. 1996a*). Similar results were also reported from the Framingham cohort (*Lin et al. 1996*).

The prevalence of AF in population-based stroke studies ranges from 15 to 34% (Jørgensen *et al. 1996a*, *Lin et al. 1996*, *Kõrv et al. 1997, Feigin et al. 1998*, *Vemmos et al. 1999*). The relative risk of stroke among subjects with AF, determined in cohort series, ranges from 5.6 to 17.6 (Jørgensen *et al. 1996a*).

It is known, that adjusted dosage of warfarin reduces primary fatal and non-fatal stroke by 62% with absolute risk reduction of 2.7%/year. The benefit of anticoagulation is even higher in secondary prevention of stroke giving a risk reduction of 8.4%/year (*Donnan et al. 2004, Leys et al. 2004*). Despite these facts, anticoagulation for stroke prevention is underused worldwide, probably due to the fear of haemorrhagic complications. However, if 1000 patients with AF are treated with warfarin for 1 year, about 2 major haemorrhages will occur, but 30 strokes will be prevented (*Donnan et al. 2004*).

Cigarette smoking. Cigarette smoking is a known risk factor for atherosclerosis, coronary events and stroke. Moreover, it has been also shown that passive exposure to cigarette smoking can be a risk factor (*Qureshi et al. 2005*). The highest prevalence of smoking in Europe is in Hungary and Poland (>40%). The prevalence of smoking in Estonia is about the EU average (30%) (*WHO 2001*).

The population-attributable risk of stroke is increased by 12% in cigarette smokers (*Hankey 2006*). The odds for stroke in cigarette smokers is increased 2 to 3-fold according to population-based and cohort studies (*Leys et al. 2004, Naess et al. 2004a, Feldmann et al. 2005, Glynn and Rosner 2005, Hankey 2006*). The prevalence of cigarette smokers among stroke patients varies from 20 to 57% in different populations (*Roose 1977, Stegmayr et al. 1997, Vemmos et al. 1999, Hadijev et al. 2003, Rodgers et al. 2004*). It has been shown that the risk of stroke in cigarette smokers is dose-dependent and cessation of smoking reduces the risk to the level of non-smokers in 2 years (*Colditz et al. 1988*).

Transient ischemic attacks. A TIA is considered a warning sign of future stroke. It gives the possibility for thorough evaluation of the patient and the introduction of all possible measures to prevent the stroke from occurring. TIA may increase the risk of stroke sevenfold and in 9 to 26% of cases a TIA precedes the stroke (*Dennis et al. 1989, Feigin et al. 1995*). In the previous stroke registry from Tartu (1991–93), 6% of strokes were preceded by a TIA (*Kõrv 1998*).

The risk of subsequent stroke after TIA is about 18% during the first 6 months (*Kleindorfer et al. 2005, Correia et al. 2006*).

It has been suggested that if all TIA patients would receive totally effective treatment, 15% of strokes could be prevented (*Hankey 1996*). Unfortunately, only about half of the TIA patients report the event to their doctor (*Dennis et al. 1989, Hankey 1996)*. This makes the management and studies of TIA even more difficult.

Hyperhomocysteinaemia. Homocysteine is a sulphur-containing intermediate product in the normal metabolism of an essential amino acid – methionine. Normally, Hcy is remethylated to methionine or is broken down into cysteine and glutathione. Those processes are catalyzed by 2 main enzymes: cystathione-β-synthase and methionine synthase and require vitamins B_6, B_{12} and folic acid as cofactors. Vitamin deficiencies and/or disturbances in enzyme function can therefore lead to hHcy (*Hankey and Eikelboom 1999*). The main cause for hHcy is considered folic acid deficiency. Elevated plasma Hcy levels are cytotoxic and are found in 5–10% of the general population and in up to 40% of patients with vascular disease (*Sacco et al. 1998, Stanger et al. 2003*). Although, the results have been inconsistent, many studies have shown a direct causal connection between thrombosis and elevated levels of plasma Hcy (*Alfthan et al. 1994*, *Verhoef et al. 1994*, *Perry et al. 1995, Boysen et al. 2003*). High Hcy levels cause thrombosis by activating blood coagulation factors, disturbing the antithrombotic function of endothelium and by inhibition of fibrinolysis. The major effects of hHcy are mediated via Hcy induced oxidative stress (*Sacco et al. 1998*, *ElKossi et al. 2000, Stanger et al. 2003*). Past studies have also indicated, that the plasma concentration of Hcy tends to decrease in the acute phase and increase in the chronic phase of stroke (*Lindgren et al. 1995*, *Meikeljohn et al. 2001, Haapaniemi et al. 2007*). As often the hHcy can be cured using vitamin supplementation, this is becoming another important modifiable risk factor for stroke (*Hankey and Eikelboom 2004; Spence 2006*).

***Cholesterol and oxidized low-density lipoprotein*.** It is known, that hypercholesterolaemia is a determined risk factor for coronary heart disease, but not for stroke (*Piechowski-Jóźwiak and Bogousslavsky 2004*). On the other hand, atherosclerosis is a known risk factor for stroke. Thus, it can be speculated that advanced atherosclerosis is presented differently in stroke patients compared to patients with ischemic heart disease. Increasing evidence supports the link between inflammation and atherosclerosis (*Lindsberg and Grau 2003, Alexandrova and Bochev 2005*). LDL accumulation in blood in this process leads to oxidized stress and modification of LDL particles. Modified particles can not metabolize normally and therefore enter the subendothelial space, where macrophages turn them into highly atherogenic oxLDL. OxLDLs are cytotoxic and induce various cellular responses such as vasoconstriction, expression of adhesion molecules and cellular proliferation (*Hulthe and Fagerberg 2002, Wallenfeldt et al. 2004*). Thrombotic strokes are characterised

by the elevated generation of free radicals and oxidative injury, leading to the promotion of lipid peroxidation (*Uno et al. 2003*).

A recent meta-analysis has clearly shown that oxLDL is a suitable marker for identifying patients at risk for cardiovascular disease (*Lobbes et al. 2006*). Uno et al. have shown that acute ischemic stroke patients have 2 times higher oxLDL levels compared to control subjects and that the peak rise in plasma oxLDL was on the 3rd day following stroke and not correlated with the severity of stroke (*Uno et al. 2003*). In their recent study, an association of elevated oxLDL levels and increased infarct size were shown and also an association with stroke severity was detected (*Uno et al. 2005*).

Despite the fact that elevated cholesterol level is not a risk factor for stroke, and that the results of several trials are conflicting, the linkage between hyperlipidaemia and stroke are still being looked for. The protective effect of statins against stroke is already known and well-studied (*Kaste 2003, Leys et al. 2004*).

C-reactive protein and fibrinogen. The role of hsCRP in stroke has been evaluated both in cohort (*Rost et al. 2001*) and cross-sectional (*Sánchez-Moreno et al. 2004*, *Masotti et al. 2005*) studies. Elevated hsCRP levels in healthy subjects increase the risk of stroke 2 to 3 times, and higher levels in stroke patients predict poor outcome (*DiNapoli et al. 2001, Rost et al. 2001*, *Sánchez-Moreno et al. 2004*, *Alexandrova and Bochev 2005*, *Masotti et al. 2005*). Meta-analysis of several studies indicates two patterns of hsCRP in stroke patients: gradually decreasing and gradually increasing levels. This finding suggests that hsCRP is not only associated with the acute phase of stroke but also indicates persistent inflammation (*Chamorro 2004, Alexandrova and Bochev 2005*).

Fibrinogen participates in clot formation and is the main determinant of blood viscosity (*Drouet 1996*) by stimulating adhesion of leucocytes to the vascular endothelium via the mechanisms of expression of intracellular adhesion molecules (*Alexandrova and Bochev 2005*). Thus, this glycoprotein has major role in the pathogenesis of cardiovascular diseases representing the inflammatory component of atherosclerosis (*Lindsberg and Grau 2003*, *Rothwell et al. 2004b*, *Alexandrova and Bochev 2005*). The persistent enhanced levels of fibrinogen in stroke survivors support the idea of the link between inflammation and atherosclerosis (*Lindsberg and Grau 2003, Alexandrova and Bochev 2005*).

Stroke is a disease with many separate independent risk factors. In addition to the above mentioned factors, many other diseases and conditions are known to be associated with stroke – e.g., various changes in blood coagulation system, anti-phospholipid syndrome, excess alcohol consumption, obesity, patent foramen ovale, pregnancy etc. Also, psycho-emotional stress (*Truelsen et al. 2003*) and poor socio-economic status (*Jakovlevic et al. 2001, Kuper et al. 2007*) may have a role in stroke development.

Most of the stroke risk factors can be modified with the help of medications and especially – changes in lifestyle. Thus, more aggressive primary prevention has still the key role in the battle against stroke. During the 1990s, the prevalence of stroke risk factors has decreased and positive changes in lifestyle have occurred in Estonia (*WHO 2001, Abina et al. 2003*).

The underlying etiological factor can be determined in most of the stroke cases, but it has been estimated, that only about two-thirds of all episodes of symptomatic atherothrombotic vascular disease can be attributed to established genetic and environmental risk factors (*Hankey 1999*). Therefore, additional causes of stroke are constantly looked for and in recent years, many of these have been evaluated in clinical research (*Hankey 2006*).

4. Arrival at the hospital and the severity of stroke

Stroke must be considered an emergency condition with a similar acute phase management as myocardial infarction. For a long time, there has been no specific treatment for acute stroke and thus stroke is not always managed as an emergency. Thrombolytic therapy for acute stroke has a very narrow time-window; therefore the analysis of patient referral times has recently become important. The effective management of stroke patients in an emergency department requires intense collaboration of neurologists, emergency doctors and radiologists (*Lindsberg et al. 2006*).

Several studies have evaluated the time and factors influencing the arrival of stroke patients at hospital (*Jørgensen et al. 1996b, Wester et al. 1999, Lacy et al. 2001, Harraf et al. 2002*). These studies show that 7 to 32% of stroke patients arrive at the hospital within the first hour from stroke onset (*Wester et al. 1999, Lacy et al. 2001, Harraf et al. 2002*). About half of the patients (35 to 61%) arrive within the first six hours from symptom onset (Table 5). Haemorrhagic stroke, older age, more severe stroke and the presence of atrial fibrillation usually contribute to faster presentation (*Jørgensen et al. 1996b, Wester et al. 1999, Lacy et al. 2001, Harraf et al. 2002*).

The reasons for presentation delays are usually patient-derived – people do not seek help hoping that the symptoms subside spontaneously. However, also in-hospital delays may contribute to limited use of thrombolysis (*Lindsberg et al. 2006*). The improvement of referral times of stroke patients is the key solution for implementing thrombolytic therapy for acute stroke all over the world. Even public educational programmes have been introduced to reduce the delay in presentation and referral of stroke patients (*Alberts et al. 1992*).

Table 5. The percentage of patients arriving at the hospital at certain time-points following stroke in selected studies

Study	Percent of patients		
	≤1 hour	≤3 hours	≤6 hours
Denmark (*Jørgensen et al. 1996b*)	7	25	35
United Kingdom (*Harraf et al. 2002*)	25	37	50
USA (*Lacy et al. 2001*)	32	46	61

The severity of stroke has been mostly evaluated in clinical trials. Unfortunately, the population-based stroke incidence studies usually do not assess stroke severity. However, the severity of stroke is directly related to case-fatality and outcome.

Several studies have assessed the severity of stroke using the SSS (*Barber et al. 2004a; Christensen and Boysen 2004; Kammersgaard and Olsen 2006*), but these studies have included selected patient groups instead of a registry-based design. Therefore, the comparison of these results is not thoroughly possible.

Generally, stroke is more severe in patients with haemorrhagic stroke and lower SSS is associated with increased short- and long-term mortality (*Christensen and Boysen 2004; Kammersgaard and Olsen 2006*) and a worse outcome (*Barber et al. 2004b*).

5. Outcome of stroke

Studies concerning stroke outcome use several different outcome measures to give a comprehensive overview of the patients' conditions at certain time points after stroke. Some reports use a population-based design (*Wolfe et al. 1993*, *Hankey et al. 2000*, *Kalra et al. 2000*, *Vemmos et al. 2000*, *Sturm et al. 2002, Appelros et al. 2003, DiCarlo et al. 2003*), some a hospital-based design (*Salgado et al. 1996*, *Pohjasvaara et al. 1997*) or just selected patients (*de Haan et al. 1995*, *Pohjasvaara et al. 1997*, *Moroney et al. 1998*, *Tilling et al. 2001*).

The most frequently used scales of disability and handicap, used in clinical trials, are the BI and mRS, respectively (*Mahoney and Barthel 1965, Wade and Langton Hewer 1987, van Swieten et al. 1988*). These scales are easy to complete and they have shown good inter-observer agreement. A profound overview of outcome after stroke can be obtained from population-based registries. Unfortunately, the lack of uniform criteria for the interpretation of the results of stroke outcome, obtained with the scales cited above and different study designs, constrain the comparison of the results from various trials.

Studies of stroke outcome using a population-based design have determined different endpoints as outcome measures. None of these reports have determined either disability or handicap scores before stroke. The studies from

England and Italy have shown that 1 to 3 months after stroke approximately 53% of patients are independent in ADL, 12 to 21% are moderately disabled and 26 to 34% severely disabled (*Wolfe et al. 1993*, *DiCarlo et al. 2003*). Severe disability in those cases is defined as the BI score below 15 (in a 20-point scale). Relatively higher proportion of patients (59%), with moderate and severe disability (defined as BI below maximum score of 20), 3 months after stroke were registered in Melbourne (*Sturm et al. 2002*). The proportion of these patients one year after stroke reduced to 51%. Another study from England reported that about 76% of patients had favourable outcome (scored 15–20 points by BI) one year following stroke (*Kalra et al. 2000*). The previous study from Tartu (*Kõrv et al*. 1999) determined the outcome of stroke at 6 months. The results showed that 82% of patients scored 15–20 points in BI and an unfavourable outcome was registered for 18% of patients (*Kõrv et al. 1999*).

In the English study, 64% of patients had a mRS score 0–2 (i.e., favourable outcome) three months following stroke, 16% had a score of 3 and 20% had a score of 4 to 5 (*Wolfe et al. 1993*). Comparable results (77% of patients scored 0–3) were also reported in the other English study (*Kalra et al. 2000*). The mRS scores one year after stroke in different populations are summarized in Table 6.

Table 6. mRS 1 year following stroke according to selected studies

Study	**Modified Rankin score, percent of patients**					
	0	**1**	**2**	**3**	**4**	**5**
England* (*Wolfe et al. 1993*)	10	24	22	17	7	4
Sweden (*Appelros et al. 2003*)	16	23	24	16	10	11
Greece (*Vemmos et al. 2000*)		69†			31‡	

*16% of patients had a score of 6 (dead)
† mRS 0 to 2
‡ mRS 3 to 5

AIMS OF THE STUDY

The main aim of the study was to study stroke epidemiology in Tartu, Estonia based on The Third Stroke Registry in Tartu, Estonia.

1. To determine the incidence and 28-day case-fatality of first-ever stroke, and the incidence of first-ever TIA from 2001 to 2003 in Tartu, Estonia and comparing the results with other studies.
2. To analyse the time-trends of stroke incidence and case-fatality in Tartu from 1973 to 2003.
3. To analyse the prevalence of risk factors, arrival time and severity of first-ever stroke in Tartu from 2001 to 2003.
4. To determine the outcome of first-ever stroke at 6 months and 1 year following stroke.
5. To determine simultaneously traditional (routine) and new markers of atherosclerosis and inflammation in the acute phase of stroke in younger stroke patients compared to healthy control subjects and to determine the associations between these biochemical markers and the outcome of stroke.

SUBJECTS AND METHODS

1. Population

By population (101 122 inhabitants), Tartu is the second largest town in Estonia. The study area is served by the DNN of the University Clinics of Tartu. Most of the population (91%) are ethnic Estonians. The proportion of people ≥65 years of age is 14%. The structure of the population according to Census 2000 (*Estonian Statistics 2000*) is presented in Table 7.

Table 7. Age and sex distribution of the population of Tartu (Census 2000)

Age group	Men	Women	Total
0–44	31095	34267	65362
45–54	4893	6141	11034
55–64	4277	6175	10452
65–74	3186	5514	8700
75–84	1166	3003	4169
≥85	309	1096	1405
Total	**44926**	**56196**	**101122**

2. Case finding

The Third Stroke Registry in Tartu was prospectively conducted from 01.12.2001 to 30.11.2003. All patients living in Tartu, who were diagnosed first-ever stroke or TIA, were registered. The Third Stroke Registry used similar study criteria as the past registries from 1970–73 (*Zupping and Roose 1976*) and 1991–93 (*Kõrv et al. 1997*).

Most of the first-ever stroke patients from the study area were routinely admitted to the DNN of the University Clinics of Tartu, where they were immediately assessed by a neurologist and where the brain CT scan was done.

For complete case ascertainment, other sources of information were also used:

1. General practitioners were contacted monthly to find the cases of first-ever stroke treated at home. The study area is served by 73 general practitioners. Three of them refused to report their possible stroke patients due to security reasons for personal sensitive data. Stroke patients treated at home received medical attention from their general practitioners and from the emergency department.
2. Medical documentation from the hospital's emergency department was evaluated twice a month. Patients who had refused hospitalisation or were

admitted to other departments of the hospital, were registered from this source.

3. Information about the cases from the other departments of the Tartu University Clinics was collected by computer search and with the help of the consulting neurologists.
4. Death certificates and autopsy reports for fatal cases outside the hospital were regularly checked. The stroke cases detected from death certificates were confirmed by contacting the physician who gave out the certificate and subjects were registered only if death was preceded by a clinical stroke according to the definition of stroke.

The study purpose and design were explained in advance to all general practitioners, on-call neurologists and to administrative specialists of other data sources.

To evaluate different stroke risk factors of younger stroke patients a case-control study was performed. The subjects, who participated in this study, were:

a. Cases: Patients less than 70 years of age consecutively admitted the DNN of the Tartu University Clinics between March 2002 and September 2003 suffering from first-ever ischemic stroke were included in the study (n=61). Patients with atrial fibrillation or valvular heart disease were excluded from the study, assuming that these conditions are apparent causes of thrombembolia and thus it would not be possible to determine the role of blood biochemical markers in the pathogenesis of stroke.

b. Controls: The control population consisted of 64 healthy subjects aged 40 to 65 years. All subjects passed a medical evaluation including a complete history and physical examination, electrocardiography and blood tests. Patients with overt coronary artery disease, valve pathologies, arterial hypertension, cerebral and/or peripheral atherosclerotic disease, diabetes, malignancies, chronic degenerative diseases and endocrine pathologies were excluded.

3. Diagnosis and subtypes of stroke

The diagnosis of stroke was based on clinical evaluation, using the WHO criteria: rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than vascular origin. Patients with SAH were included in the incidence study. Only cases of first-ever stroke were registered. The patients not meeting the study criteria were excluded.

Stroke was divided into IS, ICH and SAH according to CT findings. If the CT scan was not done, the stroke subtype was considered NC.

For the classification of IS subtypes, the TOAST criteria (*Adams et al. 1993*) were used (mainly based on clinical evaluation):

1) LAA, severe stroke of non-cardioembolic source and at least one known risk factor;
2) CE, presence of atrial fibrillation or flutter on electrocardiogram at the time of stroke onset;
3) SAO, pure motor or sensory deficit;
4) OC, coagulopathies, auto-immune disease, venous thrombosis etc.;
5) UND, despite clinical evaluation, the cause of stroke was not detected.

We classified IS mainly on the basis of case history, clinical examination and risk factor profile. The diagnosis of LAA was based on clinical symptoms of large artery occlusion and was used only in patients without atrial fibrillation or valvular heart disease.

The Scandinavian Stroke Scale (*Barber et al. 2004a*) was used to assess neurological deficit on admission and on the seventh day in hospital.

In addition, the time of stroke onset and the time of arrival at the hospital were registered.

4. Clinical data

Recorded information includes demographic and administrative data; type of stroke; concomitant diseases; use of antihypertensive and antithrombotic medications prior to stroke; clinical signs at stroke onset; CT findings etc.

Information about stroke risk factors was obtained from the general practitioners and hospital records, from the patients and their relatives.

Hypertension was diagnosed when blood pressure was constantly ≥140/90 mmHg during the first week following stroke or the patient had diagnosed hypertension and/or used antihypertensive medication prior to stroke. Atrial fibrillation or flutter and ischemic heart disease were confirmed by medical history and by electrocardiography. Diabetes was determined as known diabetes diagnosis prior to stroke or constantly elevated blood sugar levels (≥10 mmol/L) during the first week after stroke. Cigarette smoking was considered as a risk factor in current smokers.

The exact time of stroke onset and patients' arrival at the hospital's emergency department was recorded whenever possible. If the stroke was detected upon wakening, the onset time was set to the last time the person was known to be well and free of stroke symptoms.

The management of patients consisted of monitoring of vital functions and treatment of concomitant diseases, acute rehabilitation, prevention of complications and secondary prevention of stroke. The DNN did not include a geographically defined stroke unit. However, all the required therapies, interven-

tions, qualified personnel and monitoring equipment necessary to manage stroke patients, were available. Thrombolysis was not used during the study period.

5. Collection and processing of blood samples

Blood samples for biochemical analyses (collected after an overnight fast) were placed in vacuum tubes containing EDTA. Blood samples from stroke patients were drawn approximately after a week from stroke onset. Plasma was separated by centrifugation at 3000g for 15 minutes, within 30 minutes of venipuncture and stored at –25ºC until analysis. OxLDL levels were measured using an enzyme-linked immunosorbent assay kit (*Mercodia, AB, Uppsala, Sweden*). Kit's arbitrary upper reference limit is 117 U/L. Hcy levels were measured using enzyme immunoassay method (*Axis-Shield Diagnostics Ltd, Dundee, UK*).

Other blood analyses included total cholesterol, triglycerides, HDL, LDL, fibrinogen and hsCRP and were conducted immediately. Lipid levels were measured by the Hitachi 912 analyser. Plasma LDL cholesterol and HDL cholesterol (*Roche Diagnostics, Germany*), total cholesterol (*Human, Germany*), and triglycerides (*Biocon, Germany*) were measured. Fibrinogen was measured by the clotting method after Clauss using the Stago Compact analyser (*Diagnostica Stago, France*). hsCRP was determined by a validated high-sensitivity assay by using a latex particle-enhanced immunoturbidimetric assay (*Roche Diagnostics GmPh, Germany*) with the automated analyser Hitachi 912.

Reference values of other markers were as follows: total cholesterol <6.5 mmol/L, triglycerides >2.3 mmol/L, HDL >1 mmol/L, LDL < 3.3 mmol/L, fibrinogen <4 g/L and hsCRP<5mg/L.

6. Stroke outcome

The mRS prior to stroke was obtained from the patient or relatives. The functional ability of stroke patients was assessed in the hospital by registering BI scores on the 2^{nd} and 7^{th} day following stroke.

All survived patients were followed up at 6 and 12 months after stroke by a BI questionnaire sent by mail; the patients from the case-control study were assessed approximately at 1 year after the stroke. The maximum score is 20 using 1-point increments (*Wade and Langton Hewer 1987*) and indicates full independence in ADL. Study physicians also calculated mRS based on BI scores reported by the patients and their relatives. This 6-point scale (from 0 to 6) measures the overall level of handicap and the need for assistance in every-

day life. The mRS score 0 indicates full independence in every-day life and 6 means death.

7. Statistical analysis

The incidence of stroke is expressed per 100 000 persons by age and sex with corresponding 95% confidence intervals (95% CI). For the comparison of the results with that observed in other studies, rates were age-standardised (adjusted) by age to the EUR (*Ahmad et al. 2003*). The 95% CI for the rates were calculated using normal approximation to the binomial distribution. Exact confidence limits were calculated when the expected number of outcomes was less than five. The Chi-square test, stratified by gender when appropriate, was used when analysing the difference between subgroups. Mean values presented are followed by SD in the parentheses. CI for the probability of death, within 6 months after the stroke, were calculated assuming binomial distribution. The influence of prognostic factors, on the probability of death within 6 months (or one year) after the stroke, was assessed by means of logistic regression. A step-wise selection procedure was used to obtain the most parsimonious model.

The time of admission to the hospital was analysed using survival analysis techniques. Survival curves for different groups were estimated by the Kaplan-Meier method, and the groups were compared using a *P*-sample logrank test and Wilcoxon test.

For the variables of interest in the case-control study, the mean (or median) and standard deviation were calculated separately for the control and case group. A T-test and Wilcoxon ranksum test were used to compare the mean values of controls and cases. The OR and corresponding 95% CI were calculated for the groups of high and low Hcy concentration in blood. Additionally, a logistic model was found to estimate the log odds for stroke by Hcy values. The Chi-square test was used to test whether the patients, with different stroke risk factors and different types of stroke, have equal probabilities to belong in the low, medium or high Hcy/oxLDL groups. For oxLDL and Hcy linear models were considered with different sets of explanatory variables. Spearman and Kendall rank correlations and their p-values were found to study the association between variables.

All calculations were done using R (*Gentleman and Ihaka 2005*), SAS (*Der and Everitt 2001*) and S-Plus 6.2 (*Insightful Corporation 2001*).

All patients and control subjects gave informed consent before entering the case-control study. The collected data were processed according to the standing regulations of handling personal sensitive data in Estonia. The project was approved by the Ethics Review Committee on Human Research of the University of Tartu.

RESULTS

1. The Stroke Registry

The main results of The Third Stroke Registry in Tartu, Estonia are assembled in publications I to V. Paper I contains the preliminary results of stroke incidence and CFR. Paper II includes the final results of stroke incidence and case-fatality in Tartu from 2001 to 2003. Paper III analyses the time trends of stroke incidence and case-fatality compared to two previous stroke registries from Tartu. Paper IV includes data concerning the outcome of stroke 6 months and 1 year following stroke. Paper V is a summary of the main results published in the Estonian language. Paper VI presents the main results of the case-control study on stroke risk factors.

1.1. General data

During the 2-year study period, 1121 patients with diagnosis of stroke were registered. Six hundred and seventy patients (60%) were excluded because of recurrent stroke, residency out of the district, TIA (analysed separately) or final diagnosis other than stroke.

Four hundred and fifty-one patients were included in the final analysis, 182 (40%) of them were men and 269 (60%) were women. The mean age of patients was 71.6 (SD±12.3) years, 67.5 (SD±12.3) years for men and 74.3 (SD±11.6) years for women. The proportion of patients aged 65 years and older was 78%.

Three hundred and ninety-five patients (88%) were hospitalised. The majority of patients (82%) were admitted to the DNN. Cases outside the DNN were ascertained from the following data sources: 34 patients (8%) from general practitioners, 19 patients (4%) from the emergency department, 15 cases (3%) from other departments in the hospital and 12 cases (3%) from death certificates and autopsy protocols.

1.2. Diagnosis of stroke and its subtypes

The diagnosis was mainly based on a CT scan which was performed in 405 (90%) of patients. In the remaining 10% stroke was diagnosed according to clinical findings and/or autopsy results. The CT scan was without acute changes in 192 (48%) of patients (brain atrophy, silent infarctions and normal scans), 138 (34%) had acute brain infarction, 57 (14%) had ICH, 18 (4%) had SAH.

Of a total of 451 patients, 74% had IS, 13% had ICH, 4% had SAH and 9% had a NC type of stroke. The occurrence of different subtypes in each age-group are presented in Table 8.

Table 8. The frequency of different stroke subtypes in each age-group in Tartu from 2001 to 2003

Age-group	IS (N=332)		ICH (N=57)		SAH (N=18)		NC (N=44)	
	N	%	N	%	N	%	N	%
0–44	11	65	4	24	2	11	0	0
45–54	15	58	7	27	3	11	1	4
55–64	41	71	8	14	5	8	4	7
65–74	122	74	23	14	5	3	14	9
75–84	100	79	13	10	3	2	11	9
≥85	43	73	2	3	0	0	14	24

The proportion of haemorrhagic stroke subtypes decreases with age while the percentage of NC stroke increases among older subjects.

According to the TOAST criteria the subtypes of IS were as follows: LAA 26%, SAO 27%, CE 35%, UND 11% and OC 1%. The occurrence of different TOAST subtypes according to age is shown in Table 9.

Table 9. The occurrence of different IS subtypes in each age-group in Tartu from 2001 to 2003, classified according to the TOAST criteria

	LAA (N=87)		SAO (N=90)		CE (N=115)		UND (N=37)		OC (N=3)	
	N	%	N	%	N	%	N	%	N	%
0–44	3	28	5	45	0	0	2	18	1	9
45–54	3	20	6	40	1	7	5	33	0	0
55–64	7	17	14	34	13	32	7	17	0	0
65–74	36	30	37	30	38	31	10	8	1	1
75–84	25	25	21	21	45	45	9	9	0	0
≥85	13	30	7	16	18	42	4	9	1	3

1.3. Neurological deficit

Information about motor deficit was available for 432 (96%) patients, 335 (78%) of them had motor deficit: 307 (92%) of them had hemiparesis (52% of them had right and 48% left hemiparesis), 8% had monoparesis or tetraparesis. Only 11% of SAH patients had motor deficit compared to 81% of those with other types of stroke.

Information about speech disorder was available for 419 (93%) of patients, 223 (53%) of them experienced a speech disorder: 20% had dysarthria, 38% had partial aphasia, and 42% had total aphasia.

Nine (2%) patients had epileptic seizures at the onset of stroke. Ninety-five (21%) patients had disturbed consciousness at the time of stroke onset, 9% were comatose.

From the patients with IS, in 262 (79%) the stroke was clinically located in the area of *a. cerebri media*, in 41 (12%) in the brain stem, in 12 (4%) in the area of *a. cerebri anterior*, in 10 (3%) in the area of *a. cerebri posterior* and in 7 (2%) in the cerebellum. In most of the patients (73%) with NC type of stroke, the lesion was clinically located in the area of *a. cerebri media* (according to the clinical signs), 53 patients (93%) with ICH had lesion in the cerebral hemispheres, 3 (5%) in the brain stem and 1 (2%) in the cerebellum. Angiography was conducted in all patients with SAH and the underlying lesion was found in 14 (78%) of them. All detected lesions were cerebral aneurysms located in the distribution of *a. cerebri media* (22%), *a. carotis interna* (22%), *a. communicans anterior* (17%), *a. communicans posterior* (11%) or *a. basilaris* (6%).

1.4. The severity of stroke

Data concerning the SSS scores were available for 358 patients.

Both SSS0 and SSS7 scores were significantly higher for men compared to women ($p<0.05$). Also weak negative correlation between SSS0 and SSS7 scores and age ($r=–0.2$; $p<0.01$) was detected. If age was eliminated from the model, the linear correlation between SSS score and sex was no longer significant.

The SSS0 and SSS7 scores for the patients with ICH was significantly lower compared to the patients having brain infarction ($p<0.001$). The severity of stroke according to IS subtype (TOAST) was also significantly different. The most severe stroke (i.e., the lowest SSS scores) were registered for patients with CE and LAA type of stroke ($p<0.001$). As expected, the highest scores were among patients with lacunar strokes ($p<0.001$). The patients who died during the first 28 days after stroke, had significantly lower SSS scores compared to survivors ($p<0.001$).

The SSS0 score for the patients with hypertension, not using antihypertensive medication prior to stroke, was significantly lower compared to those who had used antihypertensive medication ($p<0.001$). Other registered risk factors were non-significantly related with stroke severity. Patients who had used antithrombotic treatment prior to stroke had higher SSS0 values, but the difference compared to non-users was not statistically significant ($p=0.09$).

1.5. The time of arrival at the hospital

One hundred and thirty patients were excluded from this analysis, because the exact time of the ictus was not known. Thirty-four percent of them had a NC type of stroke and 10% had stroke while they were inpatients in some other department of Tartu University Hospital. The referral data of 321 patients were used. The arrival of patients within the first 24 hours are shown on Figure 1.

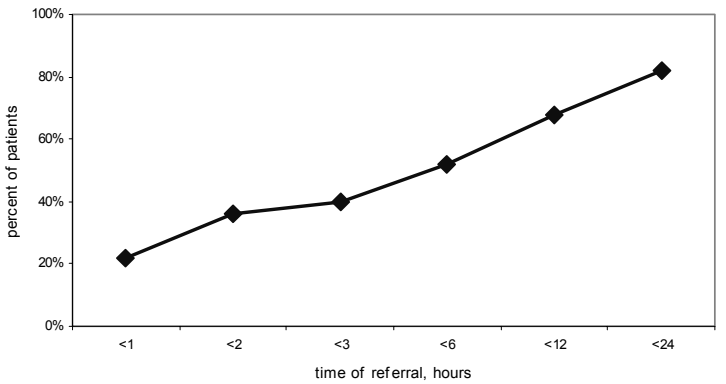

Figure 1. The cumulative percentage of first-ever stroke patients arriving at the hospital at a different time-point following stroke in Tartu from 2001 to 2003.

It was clearly seen that the patients with haemorrhagic stroke arrive at the hospital significantly faster compared to patients with IS ($\chi 2=18.8$; $p<0.001$), see Figure 2. Sixty-eight percent of patients with haemorrhagic stroke compared to 36% of patients with IS arrive at the hospital within the first 3 hours.

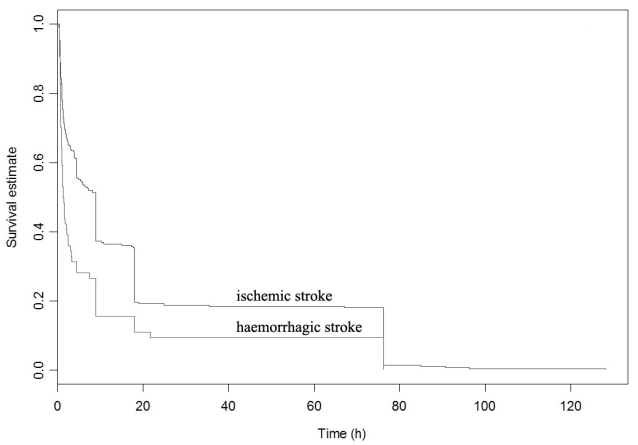

Figure 2. Time of hospital arrival of patients with different stroke subtypes in Tartu from 2001 to 2003 according to the Kaplan-Meier survival analysis.

No differences between the referral times of patients with different ischemic stroke TOAST subtypes were detected ($\chi 2=9.6$; $p=0.09$). The analysis revealed no differences in referral times between men and women ($\chi 2=0.4$; $p=0.5$). The patients with more severe stroke arrived at the hospital faster, compared to those with mild strokes ($\chi 2=25.5$; $p<0.001$), see Figure 3.

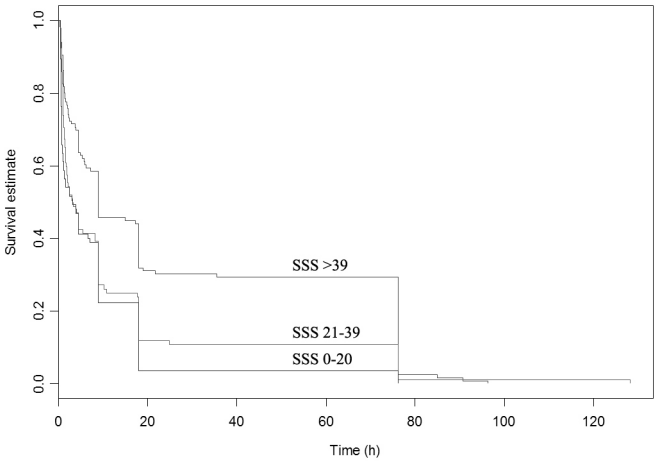

Figure 3. Time of hospital arrival of patients according to stroke severity (SSS score on admission) in Tartu from 2001 to 2003 according to the Kaplan-Meier survival analysis.

1.6. Incidence of stroke

The crude incidence rate of first-ever stroke was 223 (95% CI 203–245) per 100 000 population. The ASIR was 188/100 000 (95% CI 171–207). The crude incidence rate for men was 203 (95% CI 174–234) and for women 239/100 000 (95% CI 212–270). After standardisation, the significantly higher incidence for men became evident: 224 (95% CI 193–259) versus 164/100 000 (95% CI 144–185) for women ($\chi^2=9.3$; $p=0.002$). Age-specific incidence rates are given in Table 10.

From the age- and sex-specific incidence rates it can be seen, that the rates among men dominate in every subgroup up to the age of 75 and the rates equalise in the older age groups. The significant preponderance of the incidence rates of men compared to women, in the group of 55 to 64 years, became evident ($\chi^2=23.0$; $p<0.0001$). The incidence of different stroke subtypes are presented in Table 11.

1.7. Changes in stroke incidence

Changes in stroke incidence compared to the previous study period of 1991–1993 are presented in Table 12. The ASIR declined from 230 to 188/100 000 (p=0.04). The overall incidence rate 230 per 100 000 declined from 1993 to 2003 to 188 per 100 000 age-standardised to the EUR (p=0.04). The ASIR for men decreased from 262 to 224/100 000 (p=0.08) and for women from 204 to 164/100 000 (p=0.03). The most evident decline of the overall incidence rate was found among patients aged 45–54 (p=0.03) and 55– 64 years (p<0.01).

1.8. Incidence and trends of transient ischemic attacks

The crude incidence rate of first-ever TIA was 40 (95% CI 32–50) and the ASIR was 33/100 000 (95% CI 26–42). The crude incidence rate was almost equal both for men and women (39 vs. 40/100 000), but after standardisation the higher (but not significant) incidence for men became evident: 45 (95% CI 31–63) versus 28/100 000 (95% CI 20–38) for women (p=0.06). Age-specific incidence rates are given in Table 13.

A total of 81 patients (35 men and 46 women) with the diagnosis of first-ever TIA were registered. The mean age of the patients was 72 (±12) years. CT scan was done in 56% of the patients. The proportion of hospitalised patients was 35%. Seventy-four percent of the cases were ascertained through general practitioners and emergency department.

The age-specific trends in incidence of TIA in Tartu from 1991 to 2003 are given in Table 14. The incidence of TIA according to the ASIR has increased from 1991 to 2003. While the overall rate for women has been relatively stable, the ASIR for men has increased substantially from 28 to 45/100 000. The incidence has also increased significantly in the oldest (≥85 years) age-groups between two study periods for both men and women. The significant decline in incidence was found among women aged 55 to 64 years.

Table 10. Stroke incident cases, age-specific and age-standardised incidence rates (per 100 000) with 95% confidence intervals for men, women and total population in Tartu from 2001 to 2003

Age-group	Men			Women			All			p-value*
	No	Rate	95% CI	No	Rate	95% CI	No	Rate	95% CI	
0–44	11	18	9–32	6	9	3–19	17	13	8–21	0.2
45–54	14	143	78–240	12	98	50–171	26	118	77–173	0.3
55–64	36	421	298–583	22	178	112–270	58	278	211–359	<0.001
65–74	72	1130	884–1423	92	834	673–1023	164	943	804–1098	0.05
75–84	36	1544	1081–2137	91	1515	1220–1860	127	1523	1270–1812	0.9
≥85	13	2104	1120–3597	46	2099	1536–2799	59	2100	1598–2708	1.0
Total	182	203	174–234	269	239	212–270	451	223	203–245	0.002†
ASIR*	182	224	193–259	269	164	144–185	451	188	171–207	

* Statistical significance between the rates of men and women
† stratified by age
‡ standardised to EUR

Table 11. Incident cases and incidence rates of stroke subtypes (per 100 000) with 95% confidence intervals for men, women and total population in Tartu, 2001 to 2003.

Stroke subtype	Men			Women			Total		
	N	Rate	95% CI	N	Rate	95% CI	N	Rate	95% CI
SAH	5	6	2–13	13	12	6–20	18	9	5–14
IS	137	152	128–180	195	173	150–200	332	164	147–183
ICH	28	31	21–45	29	26	17–37	57	28	21–37
NC	12	13	7–23	32	28	19–40	44	22	16–29

Table 12. Age-specific incidence rates of first-ever stroke (per 100 000) in Tartu, in 1991–1993 and 2001–2003

Age, y	1991–1993				2001–2003				Trend per year	χ^2	p–value
All	**n**	**No in population**	**Rate**	**95% CI**	**n**	**No in population**	**Rate**	**95% CI**			
0–44	35	72124	16	12–23	17	65362	13	8–21	–2.0	0.5	0.5
45–54	75	12899	194	155–243	26	11034	118	77–173	–3.9	4.9	**0.03**
55–64	171	12074	472	407–548	58	10452	278	211–359	–4.1	12.0	**0**
65–74	187	8017	778	678–897	164	8700	943	804–1098	+2.1	3.1	0.08
75–84	256	4256	2005	1774–2266	127	4169	1523	1270–1812	–2.4	6.5	**0.01**
≥85	105	1263	2770	2289–3354	59	1405	2100	1598–2708	–2.4	3.0	0.08
Total	829	110633	250	233–267	451	101122	223	203–245			
ASIR*			230	214–246			188	171–207	–1.8	4.2	**0.04**
Men											
0–44	23	35782	21	14–32	11	31095	18	9–32	–1.6	0.3	0.6
45–54	45	5741	261	195–350	14	4893	143	78–240	–4.5	4.0	**0.04**
55–64	99	5163	639	525–778	36	4277	420	295–583	–3.4	4.7	**0.03**
65–74	74	2758	895	713–1123	72	3186	1130	884–1423	+2.6	2.0	0.15
75–84	55	1164	1576	1211–2051	36	1166	1544	1081–2137	–0.2	0.01	0.9
≥85	23	253	3034	2022–4553	13	309	2104	1120–3597	–3.1	1.1	0.3
Total	319	50861	209	187–233	182	44926	203	174–234			
ASIR*			262	232–291			224	193–259	–1.4	3.0	0.08

Table 12. Continuation

Age, y	1991–1993				2001–2003				Trend per year	χ^2	p–value
All	**n**	**No in population**	**Rate**	**95% CI**	**n**	**No in population**	**Rate**	**95% CI**			
Women											
0–44	12	36341	11	6–19	6	34267	9	3–19	–2.0	0.2	0.6
45–54	30	7158	140	98–199	12	6141	98	50–171	–3.0	1.1	0.3
55–64	72	6911	347	276–437	22	6175	178	112–270	–4.9	7.8	**0.01**
65–74	113	5260	716	596–861	92	5514	834	673–1023	+1.7	1.2	0.3
75–84	201	3092	2167	1887–2488	91	3003	1515	1220–1860	–3.0	8.3	**0.004**
≥85	82	1011	2705	2179–3357	46	1096	2099	1536–2799	–2.2	1.9	0.2
Total	510	59773	284	261–310	269	56196	239	212–270			
ASIR*			204	185–222			164	144–185	–2.0	4.6	**0.03**

* Standardised to EUR

Table 13. Incident cases, age-specific and age-standardised incidence rates of first-ever TIA (per 100 000) with 95% confidence intervals for men, women and total population in Tartu-from 2001 to 2003

Age-group	Men			Women			All			p–value
	No	Rate	95% CI	No	Rate	95% CI	No	Rate	95% CI	
0–44	0	0	0–6	1	1	0–8	1	1	0–4	0.96
45–54	3	31	6–90	3	24	5–71	6	27	10–59	0.89
55–64	6	70	26–153	3	24	5–71	9	43	20–82	0.22
65–74	10	157	75–289	14	127	69–213	24	138	88–205	0.76
75–84	12	515	266–899	19	316	190–494	31	372	253–528	0.26
≥85	4	647	176–1657	6	374	100–596	10	356	171–654	0.32
Total	35	39	27–54	46	41	30–55	81	40	32–50	0.91
ASIR*		45	31–63		28	20–38		33	26–42	0.06

* Standardised to EUR

Table 14. Trends in age-specific and age-standardised incidence rates of first-ever TIA (per 100 000) with 95% confidence intervals for men, women and total population in Tartu from 1991 to 2003

	1991–1993			2001–2003			Trend per year	χ^2	p–value†
All	**n**	**Rate**	**95% CI**	**N**	**Rate**	**95% CI**			
0–44	4	2	1–5	1	1	0–4	–5.9	0.7	0.4
45–54	10	26	12–48	6	27	10–59	+0.5	0.01	0.9
55–64	30	83	56–118	9	43	20–82	–4.8	3.0	0.08
65–74	21	87	54–133	24	138	88–205	+5.8	2.4	0.1
75–84	27	211	139–308	31	372	253–528	+7.6	4.7	**0.03**
≥85	2	53	6–191	10	356	171–654	+57.4	8.0	**0.004**
Total	94	28	23–35	81	40	32–50	+4.14	5.2	**0.02**
ASIR*		27	22–33		33	26–42	+2.2	2.8	0.1
Men									
0–44	2	2	0–7	0	0	0–6	–10.0	1.2	0.3
45–54	8	46	20–92	3	31	6–90	–3.4	0.4	0.5
55–64	11	71	35–127	6	70	26–153	–0.1	0	1.0
65–74	6	73	27–158	10	157	75–289	+11.6	2.3	0.1
75–84	9	258	118–489	12	515	266–899	+10.0	2.6	0.1
≥85	0	0	0–487	4	647	176–1657	+∞	4.9	**0.03**
Total		24	17–33	35	39	27–54	+6.5	4.6	**0.03**
ASIR*		28	20–32		45	31–63	+6.1	4.0	**0.05**

Table 14. Continuation

	1991–1993			2001–2003			Trend per year	χ^2	p–value†
All	**n**	**Rate**	**95% CI**	**N**	**Rate**	**95% CI**			
Women									
0–44	2	2	0–7	1	1	0–8	–2.0	0.03	0.9
45–54	2	9	1–34	3	24	5–71	+16.2	1.2	0.3
55–64	19	92	55–143	3	24	5–71	–7.3	5.3	**0.02**
65–74	15	95	53–157	14	127	69–213	+3.4	0.6	0.4
75–84	18	194	115–307	19	316	190–494	+6.3	2.3	0.1
≥85	2	66	8–238	6	374	100–596	+31.5	3.6	**0.06**
Total	58	32	25–42	46	41	30–55	+2.7	1.4	0.2
ASIR*		26	19–33		28	20–38	+0.8	0.1	0.8

* standardised to EUR

† Significant change between two study periods ($p<0.05$).

1.9. Stroke risk factors

Information about stroke risk factors was available for 420 (93%) of patients. The prevalence of concomitant diseases and stroke risk factors is shown on Figure 6.

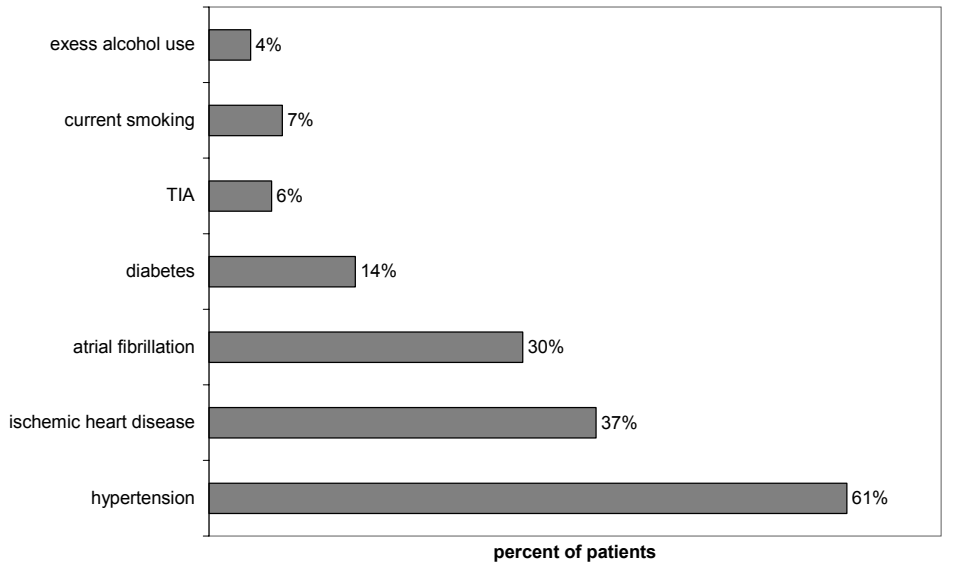

Figure 6. Prevalence of stroke risk factors among first-ever stroke patients in Tartu from 2001 to 2003.

Eight percent of patients had no risk factors. Forty-one percent of hypertensive patients did not use any antihypertensive drug prior to stroke event. Two hundred and eighty-three (67%) patients had 0 to 1, and 137 (33%) patients had 2 or more major stroke risk factors. The prevalence of risk factors according to stroke subtype is shown on Figure 5. As expected, the main risk factor for hemorrhagic stroke subtypes was hypertension. Among patients with IS, several other risk factors were also detected in most cases.

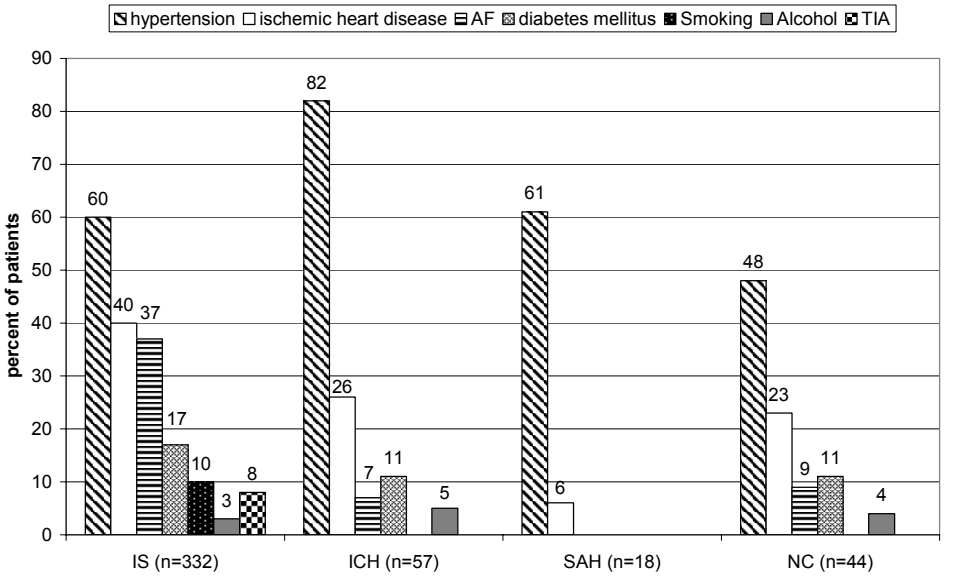

Figure 5. The prevalence of stroke risk factors according to stroke subtype in Tartu from 2001 to 2003

1.10. 28-day case-fatality of stroke

Overall 28-day CFR was 26% (95% CI 22–31), 24% (95% CI 18–31) for men and 28% (95% CI 22–33) for women. The age-specific 28-day CFR are given in Table 15.

The CFR for men in the age-group ≥85 years (62%; 95% CI 32–85) was higher compared to women (41%; 95% CI 27–57). The rate for women dominated in the age-group 45 to 54 years. None of the differences were statistically significant. The 28-day CFR among the patients aged <65 years was 16% compared to 29% among the older patients (χ^2=6.7; p=0.01).

According to the stroke subtype, the highest 28-day CFR was in the group of haemorrhagic strokes (44% for SAH and 40% for ICH); the rate for IS patients was 22% and 34% for NC patients.

1.11. Changes in case-fatality

A total of 250 (30%) patients during the previous study (1991–93) and 188 (26%) during the current study (2001–03) suffered from a fatal stroke. The age-specific CFR are shown in Table 15.

Table 15. Age-specific 28-day CFR (%) and trends (% of change) in CFR of stroke patients in Tartu, from 1991–93 and 2001–2003

Age, y	1991–1993		2001–2003		Trend per year	χ^2	p–value
Men	**n**	**CFR**	**n**	**CFR**			
0–44	0	0	2	18	1/0	4.4	0.1*
45–54	7	16	1	7	–5.4	0.6	0.4
55–64	16	16	5	14	–1.4	0.1	0.7
65–74	14	19	18	25	+3.2	0.8	0.4
75–84	23	42	10	28	–3.4	1.9	0.2
≥85	12	52	8	62	+1.8	0.3	0.6
Total	72	23	44	24	+0.7	0.002	1.0†
Women							
0–44	2	17	1	17	0	0	1.0
45–54	9	30	3	25	–1.7	0.1	0.7
55–64	13	18	4	18	+0.1	0.0002	0.9
65–74	32	28	21	23	–1.9	0.8	0.4
75–84	79	39	26	29	–2.7	3.1	0.08
≥85	43	52	19	41	–2.1	1.5	0.2
Total	178	35	74	28	–2.1	4.7	**0.03**†

* The Fischer exact p-value
† stratified by age

In most of the age-groups, the overall CFR declined between the study periods, the trend in the age-group 75 to 84 years was statistically significant (p=0.03). The number of fatal cases in younger age groups is small and moderate changes have been detected, but no statistical significance was found. The analysis of case-fatality trends according to stroke subtype revealed rather stable results, only the proportion of fatal cases among patients with ICH decreased from 57 to 40% between the studies. The overall decline in CFR did not reach statistical significance (p=0.07), but the significant decline among women (p=0.03) is responsible for this trend.

1.12. Outcome of stroke

1.12.1. Survival

Fifty-six men and 110 women had died within 6 months after their stroke and the overall probability of death at 6 months was 0.43 (95% CI 0.38–0.48).

Sixty-five men and 120 women had died at 1 year after stroke occurrence and the overall probability of death was 0.44 (95% CI 0.39–0.48).

The survival rates at 1 year (according to stroke subtypes) following stroke are shown in Table 16. The survival rates for different stroke subtypes were not statistically significantly different. The odds for death were 1.38 times higher for patients with hypertension not using antihypertensive medication prior to stroke, but the finding did not reach statistical significance (p=0.23). The odds for death for patients using antithrombotic treatment prior to stroke was also not significant (OR=0.92; p=0.8) compared to non-users.

Table 16. Survival rates at 1 year following first-ever stroke according to stroke subtypes (Kaplan-Meier analysis) in Tartu from 2001–2003

	SR*	95% CI
All strokes	0.56	0.52–0.61
Brain infarction	0.58	0.53–0.64
Intracerebral haemorrhage	0.46	0.34–0.61
Not classified stroke	0.55	0.42–0.71

* Non-significant difference of survival rates, χ^2=4.5; p=0.103

1.12.2. Follow-up

Of a total of 451 patients in the registry, 18 patients with the diagnosis of SAH were excluded and thus data from 433 patients were used in the outcome analysis; 176 (41%) of them were men and 257 (59%) were women.

Fifty percent of patients were discharged to home from the hospital, 29% were transferred to rehabilitation facilities, 5% moved to other departments of the same hospital or to a different hospital and 16% died during the hospital stay. The mean length of hospital stay was 8.6 days.

The 267 patients, surviving the first 6 months, and 246 patients, surviving 1 year after stroke, were followed up using a BI questionnaire sent by mail. Eighty-two percent of patients, for the first follow-up and 80% for the second follow-up, responded to the questionnaire (table 17).

Table 17. Proportions of patients who responded to the BI questionnaire at 6 months and at 1 year following stroke in Tartu from 2001–2003

	6 months		1 year	
	No	**%**	**No**	**%**
Questionnaires sent	267	100	246	100
Responders	218	82	194	80
Non-responders	49	18	52	20

The mean age of patients, who responded to the questionnaire at 6 months, was 69.3 (SD±11.9) years and the age of non-responders was 69.8 (SD±12.9) years (p=0.4). The corresponding values at 1 year were 68.6 (SD±11.7) and 69.7 (SD±13.0) years (p=0.3), respectively. The non-responders were more frequently (30 vs. 6%) patients with NC type of stroke (i.e. non-hospitalised patients).

For the first period, 52% of patients filled in the questionnaire by themselves and 48% of questionnaires were completed by caregivers. The corresponding numbers at 1 year were 57% and 43%, respectively.

1.12.2.1. Functional dependency

The functional dependency of patients, according to the BI score at different time-points, is shown on figure 6 (survivors and non-survivors).

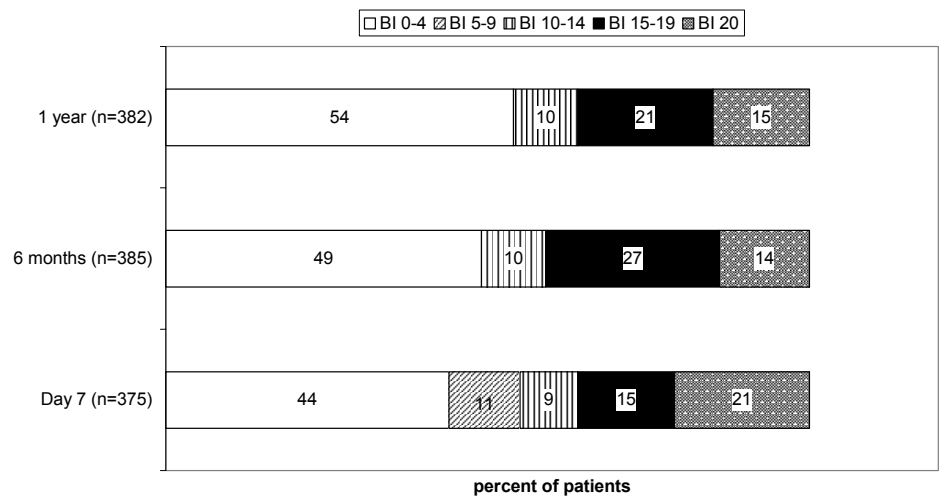

Figure 6. Functional dependency of stroke patients at different time-points after stroke according to the BI in Tartu from 2001 to 2003

Table 18 presents the percent of patients in different BI groups for patients <65 and ≥65 years of age. The chi-square test showed that disability was more profound among patients 65 years and older for all follow-up periods (p<0.001).

Table 18. Age-specific BI scores at different time-points after stroke (%) in Tartu from 2001 to 2003

BI group	2nd day after stroke		7th day after stroke		6 months after stroke		1 year after stroke	
	<65 y	≥65 y	<65 y	≥65 y	<65 y	≥65 y	<65 y	≥65 y
0–4	43	61	30	47	25	52	31	58
5–9	7	13	4	12	4	6	3	5
10–14	4	8	3	11	5	11	6	10
15–19	26	9	17	15	33	23	26	19
20	20	9	46	15	33	8	34	8

Table 19 shows the percentage of patients in different BI subgroups according to stroke subtype at different time-points after stroke. The outcome is more favourable for IS patients at every time-point compared to patients with ICH.

Table 19. The percentage of patients in different BI subgroups according to stroke subtype at different time-points after stroke in Tartu from 2001 to 2003

BI	7th day		6 months		1 year	
	IS	ICH	IS	ICH	IS	ICH
Dead	9	30	39	56	46	62
0–4	29	35	3	4	3	2
5–9	12	4	5	6	4	4
10–14	8	17	11	8	10	8
15–19	17	10	27	14	22	14
20	25	4	15	12	15	10

1.12.2.2 Handicap

The level of handicap of patients, according to the mRS score at different time-points, is shown on Figure 7 (survivors and non-survivors).

The mRS score 3 to 5 before stroke significantly increased the odds of higher mRS 6 months following stroke (OR=11.9; 95% CI 1.4–98.8). Patients in the mRS group 3 to 5 before stroke had 3.7 times higher probability of death compared to patients in the group 0 to 2 (OR=3.7; 95% CI 1.6–8.5).

The proportion of patients with a favourable outcome (mRS 0–2) at 1 year according to different stroke subtypes is shown in Table 20.

Table 20. Rates of favourable outcome (mRS=0–2) at 1 year following first-ever stroke according to stroke subtypes (Kaplan-Meier analysis) in Tartu from 2001 to 2003

	mRS 0–2*	95% CI
All strokes	0.32	0.27–0.37
Brain infarction	0.34	0.29–0.39
Intracerebral haemorrhage	0.25	0.15–0.40
Not classified stroke	0.13	0.04–0.32

* Significant difference of favourable outcome rates, χ^2=6.6; p=0.04

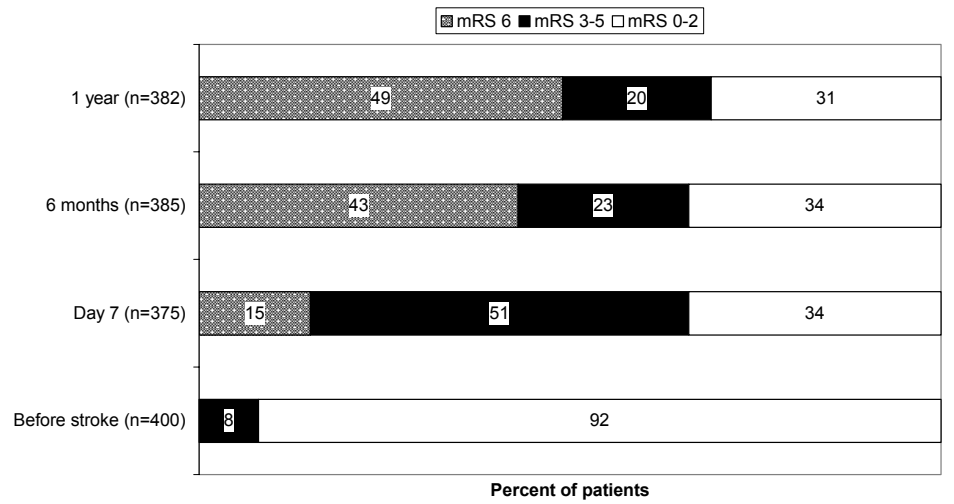

Figure 7. Level of handicap (mRS) of stroke patients at different time-points in Tartu from 2001 to 2003

1.12.2.3. Risk of dependency

Logistic regression was used to determine the risk of dependency (BI score <20) 6 months and 1 year after stroke. The results of the univariate analysis are shown in Table 21.

Table 21. Odds ratios for dependency (BI<20) according to risk factors and the severity of stroke at 6 months and 1 year following stroke using univariate regression models in Tartu from 2001 to 2003

	OR for dependency at 6 months (95% CI)		OR for dependency at 1 year (95% CI)	
Age ≥65 years	3.53	(1.78–6.97)	3.88	(1.93–7.81)
Female gender	3.30	(1.69–6.45)	2.42	(1.25–4.69)
ICH	0.67	(0.23–1.93)	1.08	(0.36–3.25)
Unclassified stroke	3.30	(0.41–26.80)	3.61	(0.44–26.69)
Atrial fibrillation	2.23	(0.96–5.15)	3.34	(1.31–8.49)
Hypertension	2.10	(1.07–4.13)	1.55	(0.77–3.14)
SSS0	0.98	(0.96–1.01)	0.96	(0.93–0.99)
SSS7	0.93	(0.88–0.99)	0.90	(0.85–0.96)

At 6 months, female sex, age, hypertension and SSS7 were found to be significant predictors of dependency. In the multivariate analysis, the model best predicting the risk of dependency consisted of the female sex (OR=2.85; 95% CI 1.43–5.69) and age (OR=3.03; 95% CI 1.50–6.11). The association with SSS7 was marginal and therefore was eliminated from the final model according to the results of the deviance test.

At 1 year following first-ever stroke female sex, age, atrial fibrillation, SSS0 and SSS7 were significant predictors of dependency. The final multivariate model included female sex (OR=2.47; 95% CI 1.12–5.44), age (OR=3.53; 95% CI 1.56–7.96) and SSS7 (OR=0.92; 95% CI 0.86–0.98) as the best predictors of dependency.

1.12.2.4. Risk of death

To analyse the independent predictors of death after stroke, univariate and multivariate regression models were used. The univariate models showed that all variables studied, (except diabetes), were significantly associated with increased odds for death 6 months and 1 year following a stroke (Table 22).

Table 22. Odds ratios for death according to risk factors and the severity of stroke at 6 months and 1 year following stroke using univariate regression models in Tartu from 2001 to 2003.

	OR for death at 6 months (95% CI)		OR for death at 1 year (95% CI)	
Age (per year)	1.06	(1.04–1.08)	1.06	(1.04–1.08)
Female gender	1.53	(1.01–2.32)	1.45	(0.96–2.19)
ICH	2.04	(1.12–3.71)	1.87	(1.02–3.42)
NC stroke	2.14	(1.01–4.53)	1.91	(0.89–4.07)
Atrial fibrillation	1.92	(1.23–2.98)	1.86	(1.20–2.88)
Hypertension	0.52	(0.34–0.80)	0.52	(0.34–0.80)
Diabetes	0.83	(0.68–2.16)	1.02	(0.57–1.82)
SSS0	0.91	(0.90–0.93)	0.93	(0.91–0.94)
SSS7	0.91	(0.90–0.93)	0.92	(0.91–0.94)

In the multivariate model, only the SSS7 and age had significant influence on death both after 6 months and 1 year following the stroke. The final model showed that a 1-point increase in the SSS7 score reduces the odds for death 1.10 times (OR=0.91; 95% CI 0.90–0.93) and 1-year increase in age increases the odds for death by 1.05 times (OR=1.05; 95% CI 1.02–1.08).

2. The case-control study of stroke risk factors

2.1. Cases

A total of 61 patients with first-ever ischemic stroke were included with a mean age of 59.0 (SD±11.5), with a range of 30–70 years. Forty-one (67%) of them were male (mean age 59.0 (SD±10.9) years) and 20 (33%) were female (mean age 59.0 (SD±12.8) years).

Two patients (3%) died within 28 days of stroke onset.

The mean time of blood sample collection was 5.7 (SD±2.4) days from the onset of stroke.

2.1.1. Homocysteine

The estimated median Hcy level was 11.2 μmol/L (range 5.6–50.9) (Table 23). As expected, the median level for men (11.7 μmol/L) was slightly higher than for women (10.1 μmol/L) ($p<0.001$). Twelve men (30%) and 10 women (48%) had Hcy values within the normal range (5–10 μmol/L); another twelve men (30%) and 5 women (24%) had Hcy values in a tolerable range (10–12 μmol/L). A total of 22 patients (36%; 16 men, 6 women) had a moderate hHcy

(>12 μmol/L). No differences were found, when comparing the results of individuals with a history of hypertension and current smokers to other patients. The mean Hcy values did not differ between ischemic stroke aetiologic subtypes. No correlation between age and Hcy value was found.

2.1.2. Oxidised low-density lipoprotein

The median oxLDL level was 117 U/L (range 52–274), no differences between the sexes were found (p=0.5) (Table 23). Twenty-two men (55%) and 10 women (48%) had plasma oxLDL levels in a normal range (<117 U/L). A total of 48% patients (18 men and 11 women) had oxLDL levels above the reference value. The median plasma oxLDL value for hypertensive patients (121 U/L) was slightly higher compared to other patients (113 U/L), but this finding was not statistically significant (p=0.3). Patients with the LAA type of stroke had significantly higher oxLDL levels (p=0.01). The levels of oxLDL were not statistically significantly different when the samples taken during the first 5 days, and samples taken later than 5 days, were compared (p=0.91). The oxLDL values did not correlate with age, stroke severity or outcome.

All the mean (or median) blood values of biochemical markers are presented in Table 23.

2.1.3. Other markers of atherosclerosis and inflammation

All the mean (or median) triglyceride, LDL and hsCRP levels were above the reference range. Six patients (10%) had plasma total cholesterol value above 6.5 mmol/L, whereas 31 patients (51%) had elevated LDL and 22 patients (36%) had HDL levels <1mmol/L. The mean LDL/HDL ratio was 3.3 (SD±1.2). High triglyceride values were found in 19 patients (31%). Triglyceride levels correlated positively with stroke severity (r=0.3; p=0.05). Twenty nine (48%) patients had elevated hsCRP levels and high fibrinogen concentration was detected in 24 patients (39%). Fibrinogen levels were negatively correlated with a SSS0 score (r=–0.2; p=0.01).

Table 23. Fasting plasma mean (±SD) or median (±MAD)* values of analysed biochemical markers in ischemic stroke patients and control subjects in Tartu from 2001 to 2003

	Men		Women		Total	
	Cases n=40	**Controls n=42**	**Cases n=21**	**Controls n=22**	**Cases n=61**	**Controls n=64**
Hcy, μmol/L*	11.7±2.1	9.6±2.4	10.1±2.2	8.1±2.6	11.2±2.2	9.1±2.6
OxLDL, U/L*	116±36	110±28	124±20	109±30	117±31	110±28
Fibrinogen, g/L*	3.9±0.8	3.0 ±0.4†	3.7±0.5	3.1±0.3†	3.8±0.7	3.0±0.3†
hsCRP, mg/L	10.4±24	1.7±1.6†	9.0±11.0	1.9±2.7†	10.0±20.5	1.7±2.0†
Cholesterol, mmol/L	5.1±1.2	5.3±0.9	5.4±0.8	5.5±1.0	5.2±1.1	5.4±1.0
LDL, mmol/L	3.2±1.0	3.5±0.8	3.5±0.8	3.4±0.8	3.3±0.9	3.4±0.8
HDL, mmol/L	1.0±0.3	1.4±0.3	1.3±0.4	1.7±0.4	1.1±0.4	1.5±0.4
Triglycerides, mmol/L*	1.8±0.6	1.0±0.3†	1.7±0.5	0.9±0.3†	1.8±0.6	1.0±0.4†

†Significant difference between cases and controls ($p<0.05$).

2.1.4. Associations with stroke outcome

Stroke outcome data are available for 52 (85%) patients. The mean time of assessment was 15±6 (12–28) months. The BI scores correlated positively with SSS7 ($r=0.7$; $p<0.001$). There was no correlation between oxLDL and Hcy values with BI or SSS7. The correlation analysis revealed that patients with lower hsCRP values had a better outcome compared to those with higher values ($r=–0.5$; $p=0.001$). A similar correlation was found between fibrinogen and BI ($r=–0.3$; $p<0.001$). Other studied parameters (triglycerides, total cholesterol, stroke subtype and concomitant diseases) had no significant effect on stroke outcome.

2.2. Controls

Sixty-four control subjects with a mean age of 53.2 (SD±7.4) were included in the study. Forty-two of them (66%) were men (mean age 53.7±7.5 years) and 22 (34%) were women (mean age 52.1±7.1 years). All control subjects demonstrated normal findings during physical examinations, and had normal blood pressure values. Seven subjects (11%) were current smokers.

2.2.1. Homocysteine

The estimated mean Hcy level was 9.1 μmol/L (range 4.6–16.7). The mean level for men (9.6 μmol/L) was slightly higher than for women (8.1 μmol/L) ($p=0.02$). Twenty-eight men (67%) and 17 women (77%) had Hcy values within the normal range; only 8 men (19%) and 3 women (14%) had Hcy values in a tolerable range. A total of 8 subjects (13%; 6 men, 2 women) had moderate hHcy. Hcy values correlated positively with age ($r=0.6$).

2.2.2. Oxidised low-density lipoprotein

No differences in oxLDL levels between sexes were found ($p=0.7$). Twenty-four men (57%) and 14 women (64%) had plasma oxLDL levels in the normal range. A total of 41% patients (18 men and 8 women) had oxLDL levels above the reference value. The oxLDL values did not correlate with age.

2.2.3. Other markers of atherosclerosis and inflammation

All the mean (or median) blood values of biochemical markers are presented in table 23. The majority of other blood markers were within the normal range. Seven subjects (11%) had a plasma total cholesterol value above 6.5 mmol/L, while 33 patients (52%) had abnormal LDL and 3 patients (5%) had HDL levels < 1mmol/L. High triglyceride values were found only in 2 subjects (3%). Three

subjects (4%) had elevated hsCRP levels and a high fibrinogen concentration was detected in 1 patient (2%).

2.3. Differences in studied biochemical markers between cases and controls

The proportion of patients in the low Hcy group was significantly lower compared to controls (χ^2=16.1; p<0.001), Figure 8. Similarly, the proportion of patients in the high Hcy group was significantly higher compared to controls (χ^2=9.0; p<0.001). The oxLDL values did not differ between cases and controls in different subgroups (Figure 9). OxLDL levels both for cases and for controls correlated positively both with total cholesterol and with LDL values (r=0.4; r=0.4).

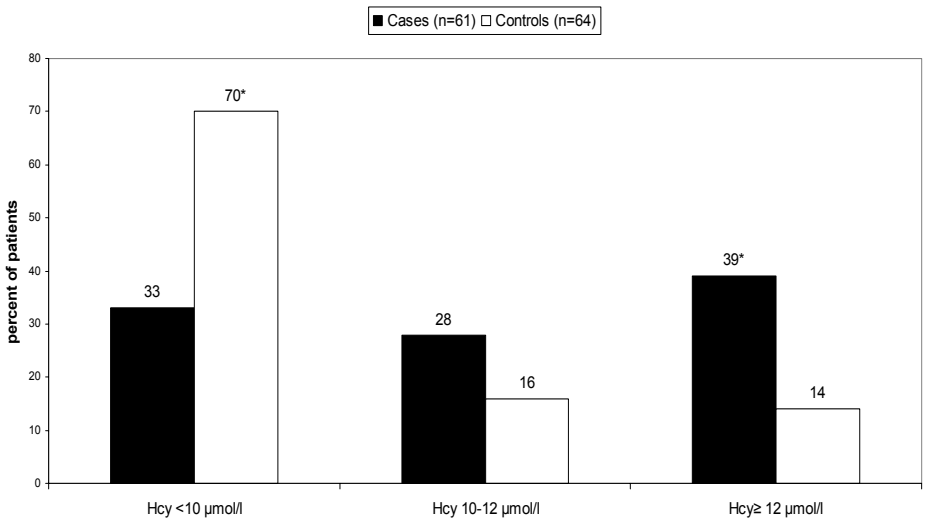

Figure 8. Percent of controls and cases in three Hcy subgroups (* denote significant difference within the group).

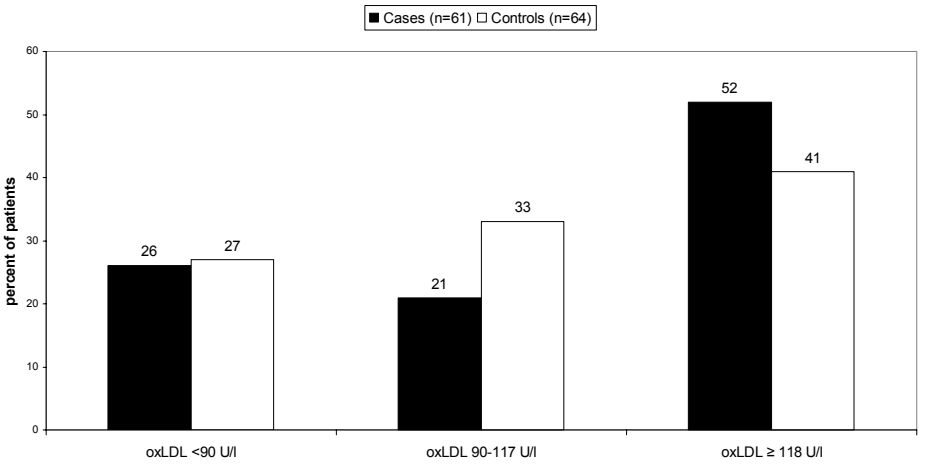

Figure 9. Percent of controls and cases in three oxLDL subgroups.

The logistic regression models showed that subjects of male gender, higher triglyceride values, older age and cigarette smoking are associated with higher Hcy values. Increased glucose, cholesterol and fibrinogen levels were related to higher oxLDL values. The multiple logistic regression model showed that the odds for higher triglyceride (OR=20.1; 95% CI 2.1–148.5), Hcy (OR=1.5; 95% CI 1.1–2.0), hsCRP (OR=1.5; 95% CI 1.0–2.3) and fibrinogen (OR=4.6; 95% CI 1.2–18.0) levels were all higher for stroke patients. The mean (or median) triglyceride, fibrinogen, Hcy, hsCRP and glucose values were significantly higher among stroke patients ($p<0.001$).

DISCUSSION

1. The Stroke Registry

1.1. General data

The integrity of stroke registries and employment of standard study criteria has always been the key issue. We have followed the study criteria presented by Sudlow and Warlow (*1996*). In our registry, the of hospitalised patients was 88 and 18% of all the cases were found outside the DNN. This fact shows the advantages of population-based studies, which in contrast to the hospital-based registries, use thorough case ascertainment and therefore enable to achieve reliable results. The proportion of cases found through different sources was similar in both study years.

A recent study from Oxfordshire recommended using a few additional data sources in stroke incidence studies (*Appelros et al 2003*). In Tartu University Clinics, brain and carotid imaging studies, due to a stroke, are conducted only after consulting a neurologist, therefore it is very unlikely that we could have received additional cases from these sources. There are still some aspects, which could have affected the completeness of our registry. Firstly, three general practitioners did not co-operate and secondly, in Estonia, the autopsy rate of patients, who die outside the hospital, is low and we could have missed some stroke patients from the oldest age-groups having a sudden death outside the hospital. The same limitation affects most of the studies of stroke epidemiology.

The proportion of stroke patients treated at home has declined since the previous study (1991–93) (*Kõrv et al. 1997*) from 19 to 12%. This result is obviously the effect of educational work since the 1970s introducing stroke as an emergency medical situation that needs to be managed in the hospital. The highest increase was accomplished between 1970s and 1980s, since the hospitalisation rate, in the first study, was only 34% (*Zupping and Roose 1976*).

When comparing the mean ages of stroke patients across populations it can be seen that Estonian men suffer from stroke 2–7 years and women 0–5 years earlier than people in other European countries (*Carolei et al. 1997, Ellekjær et al. 1997, Kolominsky-Rabas et al. 1998, Vemmos et al. 1999, Johansson et al. 2000, DiCarlo et al. 2003*), only Ukraine (*Mihálka et al. 2001*) and Georgia (*Tsiskaridze et al. 2004*) have reported a lower mean age of stroke patients.

1.2. Stroke subtype

The distribution of major stroke subtypes is comparable with the results from other studies. The haemorrhagic subtypes (ICH and SAH) are more prevalent among younger patients and the NC subtype is associated with older age (mainly non-hospitalised patients) (Table 8).

When interpreting our ischemic stroke subtypes it should be taken into account that we did not exactly follow the original TOAST criteria. In our study, the diagnosis of LAA was not based on Doppler ultrasonography, but rather on clinical signs. However, CE and SAO subtypes are diagnosed strictly following the criteria and the patients with several aetiologic factors were classified to most probable aetiologic grouping. TOAST is an aetiological classification and the large number of strokes of unknown aetiology (including patients who have several established causes for stroke) would not be very informative although widely used in clinical research. Therefore, in the group of UND stroke we have classified only patients with ischemic stroke in whom we did not find any cause for stroke despite a thorough clinical evaluation.

The analysis of IS subtypes revealed a relatively high proportion (35%) of CE strokes which is similar to the results from the Arcadia registry (*Vemmos et al. 1999*) and higher than in some other studies (*Kolominsky-Rabas et al. 1998, Tsiskaridze et al. 2004*). Another stroke study has shown the high proportion of CE strokes even among young subjects (*Ghandehari and Izadi Moud 2006*). The proportion of CE subtype increases with age (Table 9). The treatment of AF in elderly patients prior to stroke in Estonia, has possibly been inadequate. Therefore, this is the most important preventable subtype of IS and this issue needs to be addressed in stroke primary prevention methods in Estonia. The pre-stroke use of anti-coagulants in patients having AF has possibly been inadequate in Estonia. A recent study from the USA has clearly shown that increased use of anticoagulant treatment in AF results in a decrease of stroke incidence (*Lakshminarayan et al. 2006*). There were no haemorrhagic strokes due to anticoagulant therapy in our registry.

The proportion of the OC subtype is relatively low (1%) probably due to limited diagnostic facilities, especially in older age-groups. However, several other studies have also reported low frequency (0–3%) of strokes due to other causes (*McGovern et al. 1993, Brown et al. 1996, Kolominsky-Rabas et al. 1998*, *Vemmos et al. 1999*). For the same reason, the proportion of UND strokes is high in younger patients. Many of these subjects might have had their stroke due to a cause that was not found using the conventional diagnostic methods.

In a recent study, concerning stroke classification and risk factor definitions by Jackson and Sudlow (*2005*), and in the following editorial comment by Landau and Nassief (*2005*), the TOAST system receives strong criticism and we agree with the shortcomings of this classification scheme stated by the authors. The criticism mainly indicates that it is often impossible to decide which one of

the risk factors is responsible for the incident stroke. This is true and the most important point in the diagnosis of stroke should be thorough examination of the patient and the assessment and management of all the possible risk factors. Hence, the proper aetiology-based classification system for use in stroke studies should be created and adapted.

1.3. The time of arrival at the hospital and the severity of stroke

Late arrival of stroke patients is the most probable reason for underuse of thrombolytic therapy for stroke. On the other hand, effective cooperation of radiologists, neurologists and emergency medicine specialists is also a key to better management of acute stroke patients. The community should be better informed about stroke symptoms and the necessity to seek medical help as fast as possible. The effectiveness of public educational programmes, in improving the early arrival of stroke patients, has been proved (*Alberts et al. 199*2). The reasons for late arrival were not registered during this study.

The analysis showed that patients with haemorrhagic stroke arrived at the hospital significantly faster compared to the patients with IS (Figure 2). Similarly, the patients with more severe stroke arrive faster compared to those with less severe stroke (Figure 3). These two findings are closely related as the haemorrhagic stroke is usually a more severe subtype. During the past ten years, the arrival of stroke patients has significantly improved. In the previous registry (*Kõrv et al. 1997*), 67% of patients arrived at the hospital within 24 hours from stroke onset compared to 82% in the current study.

A few studies have assessed the arrival of stroke patients (*Jørgensen et al. 1996b, Goldstein et al. 2001, Lacy et al. 2001, Harraf et al. 2002*). The fastest arrival times of stroke patients were reported by the New Jersey, USA study (*Lacy et al. 2001*). The arrival times were longer in Denmark (*Jørgensen et al. 1996b*) and our results are quite similar with the study from the United Kingdom (*Harraf et al. 2002*). Similarly to our results, the studies from USA and Denmark found that patients with more severe stroke arrive at the hospital faster (*Jørgensen et al. 1996b, Goldstein et al. 2001*). The arrival times depend both on the patients and on the emergency services of a certain district. Relatively good arrival times in our study are at least partially related to a well-functioning ambulance service where stroke patients are managed as acute emergencies.

Our results show that men suffer from less severe stroke compared to women. This is related to the found correlation between stroke severity and age (women are significantly older at the time of first-ever stroke compared to men).

As expected, the severity of stroke differed among stroke subtypes and the mean SSS score for patients who died during the first month was lower

compared to those who survived. An interesting fact is that patients who did not use antihypertensive medication prior to stroke had significantly more severe stroke compared to those who had used antihypertensive medication. To our knowledge, this is the first time such association has been reported. Of course, it can not be assumed that all the patients who had used antihypertensive medications prior to stroke, had also controlled hypertension.

A recent study from USA has shown that pre-stroke use of antiplatelet agents results in less severe incident stroke (*Sanossian et al. 2006*), but an Italian study failed to confirm this fact (*Ricci et al. 2006*). This trend was also found in our study, but it did not reach statistical significance.

The SSS scale is a simple and reliable tool for estimating the severity of stroke (*Barber et al. 2004a*) and it would be advisable to use it or some other stroke severity scale, for example,. National Institutes of Health Stroke Scale (*Brott et al. 1989*) in all stroke incidence studies in order to compare different patient cohorts.

1.4. The incidence of stroke

The ASIR of first-ever stroke in Tartu was 188/100 000 (95% CI 171–207). The decline in incidence during the last decade has positioned Tartu among the centres with relatively low stroke incidence (*Kolominsky-Rabas et al. 1998, Johansson et al. 2000, Wolfe et al. 2000, DiCarlo et al. 2003, Tsiskaridze et al. 2004)*, the rates in other populations (*Bonita et al. 1995, Carolei et al. 1997, Ellekjær et al. 1997, Vemmos et al. 1999, Mihálka et al. 2001*) are somewhat higher. While the incidence rates among women in Tartu are quite similar compared to the results from other studies, the rates for men are generally much higher (Tables 24 and 25), especially in younger age-groups.

The highest incidence rates are especially among men in the age-groups 55–64 and 65–74 years. Based on the results also from the two previous stroke registeries from Tartu we assume, that Estonian patients suffer from stroke at younger ages compared to most other populations. The stroke incidence rates equalize with other populations among men aged ≥75 years as most men in our population suffer from stroke during their younger ages. The incidence rate for women aged 55–64 years is lower compared to most other populations (Table 25). The higher incidence of stroke among young population is usually reported from Eastern European countries (*Kõrv et al. 1997, Mihálka et al. 2001, Tsiskaridze et al. 2004*). A recent study from Iran has also reported high incidence of stroke among subjects aged 15 to 44 years which is comparable with our results (*Ghandehari and Izadi Moud 2006*). Rates in older age-groups are comparable with other populations. This fact again proves the importance of including older persons of the community in stroke incidence studies and

Table 24. Age-specific rates and ASIRs (standardised to EUR) for stroke (per 100 000) in men in selected populations in the 1990s

Age group (years)	0–44	45–54	55–64	65–74	75–84	≥85	Total	ASIR
L'Aquila (*Carolei et al. 1997*)		107	294	969	1682	3632	276	362
Uzhgorod (*Mihálka et al. 2001*)	43	501	1026	1635	3514	0	319	
Arcadia (*Vemmos et al. 1999*)		113	240	662	1275	3219	367	
Erlangen (*Kolominsky-Rabas et al. 1998*)	16	128	188	610	1288	2415	147	148
Inherred (*Ellekjær et al. 1997*)	13‡	60	223	727	1994	3346	285	
Lund-Orup (*Johansson et al. 2000*)	1*	58†	375	965	1742	1651	201	194
Dijon (*Wolfe et al. 2000)*	7	41	217	718	960	1832	141	131
London (*Wolfe et al. 2000)*	10	109	293	614	974	2087	131	147
Vibo-Valencia (*DiCarlo et al. 2003*)	7	62	175	785	1854	2162		165
Auckland (*Bonita et al. 1995*)		104	423	1132	2078	1665		
Tbilisi (*Tsiskaridze et al. 2004*)	20	127	328	783	994	1119	159	163
Tartu (*Kõrv et al. 1997*)	21	261	639	895	1576	3034	209	262
Tartu (2001–2003)	18	143	421	1130	1544	2103	203	224

* age-group 15 to 34 years
† age-group 35 to 54 years
‡ age-group 15 to 44 years

Table 25. Age-specific rates and ASIRs (standardised to EUR) for stroke (per 100 000) in women in selected populations in the 1990s

Age group (years)	0–44	45–54	55–64	65–74	75–84	≥85	Total	ASIR
L'Aquila (*Carolei et al. 1997*)		81	171	699	1520	2479	274	
Uzhgorod (*Mihálka et al. 2001*)	13	276	502	1367	2130	1116	246	
Arcadia (*Vemmos et al. 1999*)		48	196	478	1166	2137	316	276
Erlangen (*Kolominsky-Rabas et al. 1998*)	17	81	203	437	1197	2013	201	125
Inherred (*Ellekjær et al. 1997*)	11‡	19	209	701	1697	2882	338	
Lund-Orup (*Johansson et al. 2000*)	3*	46†	196	469	1296	1916	187	126
Dijon *(Wolfe et al. 2000)*	11	49	133	263	705	1293	134	81
London (*Wolfe et al. 2000)*	8	73	139	390	895	1904	128	104
Vibo-Valencia (*DiCarlo et al. 2003*)	12	77	125	392	1189	1980		115
Auckland (*Bonita et al. 1995*)		97	256	712	1789	3287		
Tbilisi (*Tsiskaridze et al. 2004*)	4	38	384	670	1046	1014	171	139
Tartu (*Kõrv et al. 1997*)	11	140	347	716	2167	2705	284	204
Tartu (2001–2003)	9	98	178	834	1515	2099		164

* age-group 15 to 34 years
† age-group 35 to 54 years
‡ age-group 15 to 44 years

shows that general comparison of overall rates does not always characterise the real situation. Higher incidence of stroke among young persons in Eastern Europe could be explained by lower quality of life, less attention to public health, high prevalence and/or poor control of stroke risk factors which probably result in early stroke. High level of stress caused by an unstable community and socioeconomic situation, can also be related to higher incidence of stroke in Estonia. The possible genetic differences, as a plausible cause of higher stroke incidence in Eastern Europe, remain to be studied.

1.5. Changes in stroke incidence

The previous stroke registries in Tartu from 1970 to 1973 and 1991 to 1993 (*Zupping and Roose 1976*, *Kõrv et al. 1997*) have shown relatively high stroke incidence and 28-day CFR. Although the design of all three studies has been similar, the implement of CT and computerised databases from 1990s have specified the diagnosis of stroke subtypes, simplified data collection and apparently improved the completeness of case ascertainment. Identical data collection methods have been used in all three studies and two authors of this paper have also conducted the earlier stroke registries in Tartu.

The incidence of first-ever stroke in Tartu has declined significantly during the past decade and reached the level of the 1970s (*Zupping and Roose 1976*). Analysis of different age-groups revealed, that for both sexes, in most groups, the incidence has declined (Table 12). However, among patients aged 65–74 years a slight increase was assessed, but that change was not statistically significant. The remarkable decline in incidence rates, during the past ten years, was observed in patients aged 55–64 years both for men and for women, also in men aged 45–54 years and in women aged 75–84 years. The reason for such a decrease in stroke incidence may be the result of improved primary prevention, changes in lifestyle and, and as a consequence, patients suffer from stroke probably in older ages. On the other hand, the incidence among younger age-groups, representing people of working age in Estonia, remains high. Moreover, recent public data show that the life expectancy among Estonian women is about 5 years, and among men more than 10 years, shorter compared to the European Union average (*WHO 2001*). The proportion of elderly inhabitants, in the study area, has increased between the last two study periods, which would have increased the crude incidence rate. One can speculate that the overall decline of the incidence rate could be related to the improvement of primary prevention, especially antihypertensive treatment in the 1990s. The introduction of CT, explained by other authors as a possible reason for the increase in the detection of less severe strokes, can be related to the increasing stroke incidence rates. This phenomenon can not be seen in our study as the proportion of CT

scanning was higher for the second study, but the incidence has declined substantially.

1.6. Incidence of TIA

The incidence of TIA in Tartu is somewhat higher compared to the results from other studies (*Whisnant et al. 1973, Dennis et al. 1989, Bejot et al. 2007*), but also higher rates have been reported (*Ricci et al. 1991, Rothwell et al. 2004a, Kleindorfer et al. 2005, Correia et al. 2006*). In Tartu, the incidence of TIA has changed from 33/100 000 in the 1970s and from 28 to 40/100 000 in the 1990s. During the past ten years, the significant increase in the incidence was observed in the oldest age-groups, both among men and women.
The reasons for the increasing trend of TIA are hard to explain. However, it could be related to case-finding methods and improvement of diagnostic methods of TIA.

1.7. Stroke risk factors

The prevalence of stroke risk factors has wide geographical variations. The pattern of risk factor profiles in different populations provides information about stroke aetiology and directs primary prevention.

The proportion of CE strokes due to AF (30%) is comparable with the results from the Arcadia registry (*Vemmos et al. 1999*) and is much higher compared to other centres: 18% in Copenhagen (*Jørgensen et al 1996a*), 20% in Framingham (*Lin et al. 1996*), 25% in Tartu according to the previous registry (*Kõrv et al. 1997*) and 15% in Novosibirsk (*Feigin et al. 1998*). These comparisons indicate that AF is a major problem in Estonia and the incidence of stroke can be lowered by the effective and aggressive treatment of AF with anticoagulation, which has so far not been sufficient.

The prevalence of diabetes in stroke patients has remained constant compared to the previous registry from Tartu (12 and 14%) and is in the modest range compared to other populations (*Jørgensen et al. 1994a, Stegmayr and Asplund 1995, Feigin et al. 1998, Vemmos et al. 1999, Rodgers et al. 2004*).

The proportions of smoking, cardiac diseases and alcohol consumption were relatively low. This fact can also be related to study methodology issues. For example, some patients might not report being smokers or this information can not be obtained due to aphasia or unconsciousness.

The latest comprehensive information on major health indicators in Estonia is available from WHO databases (*WHO 2001*). Blood pressure trends have been evaluated in an Estonian longitudinal study including subjects aged 20 to 54 years. The analysis of three independent random samples, from different

time points, revealed a substantial decrease in blood pressure values by the early 1990s and this trend continued to a smaller extent during the late 1990s (*Abina et al 2003*).

The prevalence of hypertension among stroke patients in Tartu is relatively low (61%) compared to some other populations: 85% in Novosibirsk (*Feigin et al. 1998*) and 81% in Arcadia (*Vemmos et al. 1999*). The prevalence of hypertension among stroke patients was 50% in 1991–93 and 61% in 2001–03. However, as the cut-off points were different (165/95 mmHg and 140/90 mmHg, respectively), the trend can not be estimated. The prevalence of cigarette smokers in Estonia is high. In 1998, 42% of men and 20% of women were regular smokers. These proportions were on the highest level in 1994 and have constantly declined, but remain somewhat higher than the EU average. Cigarette smoking is more prevalent among middle-aged subjects (61% of men and 29% of women aged 35–49 years) (*WHO 2001*). The Baltic Nutrition and Health Survey has shown a favourable trend in the nutritional status during the 1990s – the use of butter on bread has decreased from 90 to 27% and the use of vegetable oil in cooking has increased from 21 to 84% from 1990 to 1998. Still, the blood cholesterol levels remain high in the Estonian population – 30% of men and 31% of women aged 34 to 64 years have increased cholesterol levels (*WHO 2001*). The study evaluating blood pressure changes revealed also a positive trend of decreasing body mass index during the 1990s (*Abina et al. 2003*). As a consequence, the overall trends in risk factor profiles can be considered positive and the decline in the stroke incidence and CFR can be associated with this trend.

1.8. 28-day case-fatality

The overall 28-day CFR of stroke in Tartu is 26%. This is similar to the results from several other studies (*Carolei et al. 1997, Vemmos et al. 1999, Wolfe et al. 2000, Truelsen et al. 2002*), but remains higher compared to many other centres (*Ellekjær et al. 1997, Kolominsky-Rabas et al. 1998, Mihálka et al. 2001, DiCarlo et al. 2003*) (Figure 10). The overall rate for women is somewhat higher, but analysis of different age-groups revealed no statistically significant differences between sexes.

The CFR for haemorrhagic strokes is always significantly higher compared to IS patients. The CFR for ICH (40%) in our population is the lowest compared to other centres (*Carolei et al. 1997, Kolominsky-Rabas et al. 1998, Vemmos et al. 1999, DiCarlo et al. 2003*), only Norway has reported a somewhat lower rate (38%) (*Ellekjær et al. 1997*). The 28-day CFR for SAH (44%) is comparable with other centres, only Italy (*Carolei et al. 1997*) has a considerably lower rate (29%) compared to others. The 28-day CFR for IS ranges from 11 to 22% our rate being the highest. Case-fatality of patients with NC type of stroke varies

also and is probably related to case ascertainment methods, completeness of registry and the organisation of stroke services. The rate ranges from 25 to 69% in different populations (*Carolei et al. 1997*, *Ellekjær et al. 1997*, *Kolominsky-Rabas et al. 1998*, *Truelsen et al. 2002*, *DiCarlo et al. 2003*). The rate of NC type of stroke in our study was 34%.

The high 28-day case-fatality of stroke (especially IS) patients in Tartu is probably related to severe stroke cases and the poor health status of patients prior to stroke. In our study, 41% of registered patients with hypertension did not use antihypertensive medication and interestingly, patients who did not use medication had more severe stroke compared to others. The management of stroke in the hospital is highly effective and patients die due to severe stroke rather than due to the secondary complications of stroke.

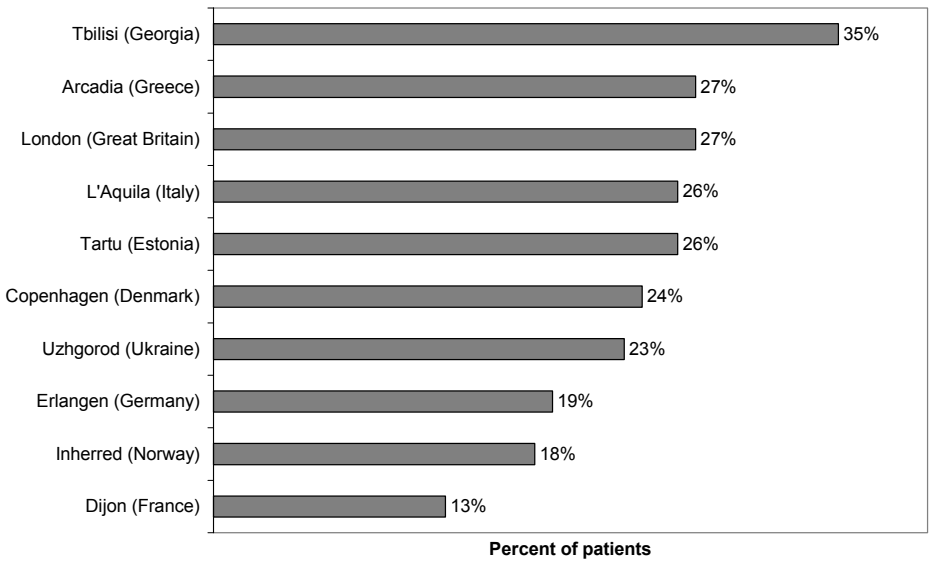

Figure 10. 28-day CFR in different populations.

1.9. Changes in case-fatality

The changes in 28-day CFR in Tartu from 1970 to 2003 are comparable with the trends in incidence rates. During the 1980s, the incidence rose but probably as a result of increased hospitalisation (from 34 to 72%) the overall CFR decreased substantially. The overall 28-day CFR in the 1970s, was 49% (*Zupping and Roose 1976*) and has declined from 30 to 26% during the past decade. The analysis of 28-day case-fatality in different age groups revealed no statistically significant changes (Table 15).

The management of stroke in Tartu has always been in correspondence with generally approved guidelines. There might have been more aggressive prevention strategies for secondary complications of stroke during the 1990s and as a consequence the 7-day CFR has declined from 15% in 1993 to 12% in 2003. The 7-day CFR during the first registry in 1973 was 31% (*Zupping and Roose 1976*).

Estonian official mortality data also show, that the standardised mortality rate of cardiovascular and cerebrovascular diseases gradually increased from the end of the 1980s to the mid-90s (*Estonian Statistics 2000, WHO 2001*). The years of significant socio-economic changes causing stress and instability in the Estonian population in the beginning of the 1990s coincide the second study in 1991–93. The mortality rates, according to the official statistics, decreased to the level of the 1980s by the end of the 1990s. The stroke mortality rates continued to decline in the turn of the century. This trend coincides with the positive changes in the incidence and CFR found in our study, thus shows that they are real. The improved management of stroke and risk factors has probably resulted in continuous decline both in the incidence and CFR of stroke in Tartu.

1.10. Outcome of stroke

The outcome of stroke was assessed using well-known outcome scales – the Barthel Index and the Modified Rankin Scale. The scales were completed both during the hospital stay, 6 months and 1 year following the first-ever stroke. Different measures were used to gain a comprehensive overview of patients' outcome from a different point of view. The proportion of responders to the follow-up questionnaire was 82% at 6 months and 80% at one year. The reasons for not responding are not known. The relatively high proportion of patients, lost to follow-up, is partially related to serious restrictions for processing personal sensitive data in Estonia (*Rahu and McKee 2003*). If the patient did not respond, a second questionnaire was sent. If still no response was obtained, we considered that the patient did not want to share his/her personal information with us. Unfortunately, the small response rate is not very rare in population-based studies (*Sturm et al. 2002, Weimar et al. 2002*), but these studies characterise the outcome of all stroke patients from a community rather than only a certain group of hospitalised patients. No differences were found between responders and non-responders, and thus we suppose that the results represent the whole sample of the patients.

Our sample consists of somewhat younger patients compared to other community-based stroke populations studied (*Hankey et al. 2000, Kalra et al. 2000, Vemmos et al. 2000, Appelros et al. 2003*). This is assumably caused by the fact that Estonian patients suffer from stroke several years earlier, compared to many other European populations and incidence rates are higher in younger

age groups. The baseline characteristics (stroke subtypes and concomitant diseases) were comparable between different study centres (*Kalra et al. 2000, Vemmos et al. 2000, Sturm et al. 2002*). Hence, the Swedish study (*Appelros et al. 2003*) reported a somewhat lower prevalence of hypertension, and lower 28-day CFR, compared to others.

Favourable outcome (BI score 20) at 6 months among those who responded to the questionnaire was found for 25% of patients in our study, 38% in the previous study from Tartu (1991–93) (*Kõrv et al. 1999*) and 49% in the Australian registry (*Sturm et al. 2002*). The lower proportion of patients with favourable outcome in Tartu (both in 1991–93 and 2001–03) and lower survival rates at 1 year compared to the Australian registry (54%, 56% and 63%, respectively) could be associated with more severe stroke in our population.

The proportion of survived patients with favourable outcome according to the mRS score in our study was 69% compared to 70% in the Greek registry (*Vemmos et al. 2000*) and 74% in the UK study (*Kalra et al. 2000*). However, the percentage of handicapped patients is somewhat lower compared to others (*Kalra et al. 2000, Appelros et al. 2003*). We speculate that more severe stroke patients just die because of insufficient rehabilitation possibilities, while those who survive are not so dependent on outside care.

The predictors of dependency following stroke were older age, female sex, higher blood glucose levels on admission and more severe stroke. Similar results have been reported in some other studies (*Kõrv et al. 1999, Vemmos et al. 2000, Appelros et al. 2003*).

The probability of death at 1 year is comparable with the previous study from Tartu (*Kõrv et al. 1999*), but is somewhat higher than in other centres (*Vemmos et al. 2000, Sturm et al. 2002*, *Appelros et al. 2003, Liu et al. 2006*). The higher death rate at 1 year can partially be explained by more fatal stroke cases at the acute stage in Tartu.

The 1-year survival rates for first-ever stroke patients range from 63% (*Vemmos et al. 2000, Hardie et al. 2005*) to 86% (*Liu et al. 2006*). Both the mean age of patients in our study and the median 1-year survival rate is lower (56%) compared to other studies (*Vemmos et al. 2000, Hardie et al. 2005, Liu et al. 2006*). In addition, the outcome of younger patients is also worse compared to other studies. A Norwegian study (*Naess et al. 2004b*) of young IS patients aged 15 to 49 years, reported that long-term (mean time 5.7 years) favourable outcome (mRS≤2) was 79%. The authors conclude that although the majority had a favourable functional outcome, cerebral infarction had major long-term impact on young adults as evaluated by mortality, recurrence and employment status. The corresponding mRS rate in our sample at 1 year was only 58%.

Recent studies from China (*Liu et al. 2006*), also Greece (*Vemmos et al. 2000*) and Sweden (*Appelros et al. 2003*), have shown significant differences in 1-year survival of different stroke subtypes. This trend was also seen in our

sample, but the differences did not reach statistical significance, probably due to the small number of cases (Table 16).

Although there are no comparative data, we still suggest that stroke is more severe in Estonia (lower proportion of independent patients and lower survival rate at 1 year). It can be speculated that according to our results, intensive treatment of blood pressure and anti-coagulant use for patients with AF before stroke not only can decrease the incidence, but can also reduce the stroke severity and thereby improve the outcome of stroke. The fact that none of our 451 patients in the registry were on anticoagulants is surprising, but shows clearly that this might be the main shortage in the primary prevention of stroke in Tartu. The use of anti-coagulation can increase the number of ICH with bad prognosis, but the improvement of overall outcome of stroke should probably outweigh this risk (*Donnan et al. 2004*). Moreover, CE strokes are usually severe and have a worse outcome compared to other subtypes of stroke (*Candelise et al. 1991, Lin et al. 1996*). The functional independency after stroke is achieved with qualified acute therapy and especially with an adequate rehabilitation program. However, the goal is to prevent stroke from happening, and therefore it is necessary to intensify the primary prevention of stroke.

2. The case-control study

The results of the case-control study show significant differences in Hcy, triglyceride, hsCRP and fibrinogen concentrations, but not in oxLDL (the aldehyde-modified form) values between control subjects and acute stroke patients less than 70 years of age.

2.1. Homocysteine

The role of hHcy in the development of cardiovascular disease has been extensively studied, but many issues are still unsolved. Howard et al. (*2002*) have shown that Hcy blood concentrations are lower in the acute phase of stroke and continue to rise thereafter. Our results show that stroke patients have significantly higher Hcy values compared to healthy controls. Assuming that the Hcy levels are higher in the chronic phase, this difference could be even more pronounced. The lower values of Hcy, in the acute phase of stroke, could be the basis for why several studies have failed to show any difference in Hcy levels between acute stroke patients and controls (*Meikeljohn et al. 2001, Yang et al. 2004*). For some reasons, the mean Hcy values in our group were somewhat higher compared to other studies (*Meikeljohn et al. 2001, Yang et al. 2004*), although El Kossi and Zakhary (*2000*) have reported much higher values.

It has been estimated that effective reduction of elevated plasma Hcy by 3 to 5 µmol/l might reduce the relative risk for cardiovascular disease by 10% in the general population and by 25% in high-risk groups (*Stanger et al. 2003*). Although the results of the 'Vitamins in Stroke Prevention trial' did not show significant difference in the cumulative incidence of recurrent cerebral infarction, hHcy still remains a treatable risk factor for stroke and while awaiting the results of ongoing trials, patients of hHcy should be treated with folic-acid based multivitamins (*Stanger et al. 2003*).

2.2. Oxidised low-density lipoprotein

Our goal was to investigate the role of oxLDL at a more conditionally sub-acute period of stroke (5 to 6 days). The significantly higher oxLDL values of stroke patients compared to controls was not confirmed in our sample. But similarly to the study by Faviou et al. (*2005*) , the oxLDL levels correlated positively both with LDL and total cholesterol values. The mean time of oxLDL determination was 5.7 days and therefore we could have missed the peak concentration reported by Uno et al. (*2003*). On the other hand, Polidori et al. (*1998*) showed that the peak concentration of lipid peroxidation index occurred on day 5 following stroke and it was positively correlated with the severity of stroke. Forty-one percent of our healthy controls had elevated oxLDL values which could indicate a relevant problem considering the pathogenesis of atherosclerosis in the whole population. In addition, we showed that patients with the LAA type of stroke had significantly higher oxLDL values compared to other subtypes which indicates strong relationship between oxLDL and atherosclerotic changes. This has also been shown by other studies (*Ryglewicz et al. 2002, Uno et al. 2003*). The results did not depend on concomitant risk factors of stroke patients. The systemic review, conducted by Lobbes et al. (*2006*), showed that the relative risk of death and coronary events increases with increasing levels of oxLDL (OR 1.9 to 3.2) according to some case-control and cohort studies. Our follow-up period was shorter compared to previous studies and the levels of oxLDL (the apoB100 aldehyde-modified form) in our study did not predict stroke outcome.

2.3. hsCRP, fibrinogen and triglycerides

The elevation of hsCRP and fibrinogen in stroke patients is anticipated and related to the systemic changes and the development of ischemic brain damage. As many as 48% of stroke patients had elevated hsCRP levels compared to 4% of control subjects.

In our study sample only 1 control subject had elevated fibrinogen level compared to 24 patients. Both high fibrinogen and hsCRP levels were associated with unfavourable outcome at 1 year. Similar findings were also reported by Di Napoli et al. (*2001*). Moreover, both markers were significantly higher in stroke patients and correlated with stroke severity. As we studied patients with acute stroke, it is not known whether these changes reflect only the acute stage or were the levels also elevated prior to stroke.

Two studies have demonstrated that lower triglyceride values in stroke patients predict poor outcome and more severe stroke (*Weir et al. 2003, Dziedzic et al. 2004*). In our sample, we found a weak positive correlation between stroke severity and triglyceride levels and no association of triglyceride levels with the outcome of stroke.

One possible limitation of our study could be the age-difference of cases and controls. Nevertheless, in none of the multiple regression models age was found to be in an association with the studied biochemical markers. Moreover, the reference values of biochemical markers are the same regardless of patient's age.

It can be concluded that conventional inflammatory markers (hsCRP and fibrinogen) are important factors showing the severity and outcome of stroke. At the same time a certain elevation of oxLDL (the apoB100 aldehyde-modified form) and Hcy levels did not act as a direct sign for first-ever ischemic stroke severity and outcome in our sample. Hence, we found that there may exist some links between the LAA subtype of ischemic stroke and elevated oxLDL levels. We chose to use the validated ELISA method (*Holvoet et al. 1998a, Holvoet et al. 1998b*) for the detection of plasma oxLDL and Hcy in stroke patients. It is possible that evidently some other form(s), not the apoB100 aldehyde-modified form, of LDL reflects directly severity and outcome of acute ischemic stroke. Thus, the role of oxLDL, especially its different forms, as a possible acute stroke-linked marker of systemic oxidative stress must be thoroughly identified in further studies assessing stroke severity, subtype and outcome.

CONCLUSIONS

1. The crude incidence rate of first-ever stroke was 223/100 000, and the ASIR was 188/100 000. The crude incidence rate for men was 203 and for women 239/100 000. After standardisation, the significantly higher incidence for men became evident: 224 versus 164/100 000 for women. When compared to other studies, the incidence of stroke in younger age-groups is significantly higher in Tartu.
2. The proportions of major stroke subtypes was comparable to other studies: 74% had IS, 13% had ICH, 4% had SAH and 9% had a NC type of stroke. The results show, that the proportion of CE strokes was relatively high and probably indicates inadequate treatment of atrial fibrillation with anticoagulants in Estonia. The prevalence of other ischemic stroke subtypes was comparable with the results from other studies.
3. The crude incidence rate of first-ever TIA was 40/100 000 which is comparable to results from other populations. The age-standardised rate was 33/100 000. The crude incidence rate was almost equal both for men and women (39 vs. 40/100 000).
4. During the past 10 years, the ASIR of stroke has decreased from 230 in 1993 to 188/100 000 in 2003. This corresponds to the level of incidence reported for the period 1970 to 1973. The ASIR for men decreased between 1991 to 2003 from 262 to 224, and for women from 204 to 164/100 000. The most evident decline of the age-specific incidence rate was found among patients aged 45 to 54 and 55 to 64 years, i.e., among the subjects in working-age.
5. Overall 28-day CFR was 26%, 24% for men and 28% for women. According to the stroke subtype, the highest 28-day CFR was in the group of haemorrhagic strokes (44% for SAH and 40% for ICH); the rate for IS patients was 22% and 34% for NC patients. During the past 10 years the CFR has declined from 30 to 26%.
6. Stroke was more severe among men and among elderly subjects. Patients with haemorrhagic stroke subtypes had more severe stroke compared to others. Forty percent of patients arrived to hospital within 3 hours from symptom onset; the corresponding proportion at 12 hours was 68%. Patients with more severe stroke arrived significantly faster compared to those with less severe stroke.
7. Thirty percent of patients had AF, 61 % had hypertension, 14% had diabetes, 37% had ischemic heart disease, 6% had previous TIA and 7% were current smokers. Eight percent of patients had no risk factors.
8. According to the BI questionnaire sent to patients to assess stroke outcome, the proportion of totally independent (in activities of daily living) patients at 6 months was 41% and 36% at 1 year. The post-stroke disability was more profound among patients 65 years and older for all follow-up periods

compared to younger patients. At 1 year following first-ever stroke female sex, age and SSS7 were significant predictors of dependency.

9. The results of the case-control study showed significant differences in Hcy, triglyceride, hsCRP and fibrinogen concentrations, but not in median oxLDL values between control subjects and acute stroke patients in our sample. However, patients with LAA type of stroke had significantly higher oxLDL level compared to other subtypes which indicates strong relationship between atherosclerotic changes and oxLDL. As many as 48% of stroke patients had elevated hsCRP levels compared to 4% of control subjects and only 1 control subject had an elevated fibrinogen level compared to 24 patients. Both high fibrinogen and hsCRP levels were associated with unfavourable outcome at 1 year.

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SUMMARY IN ESTONIAN

Kolmas Tartu insuldiregister 2001–2003: haigestumus, letaalsus, riskitegurid ja hilistulemused

Kokkuvõte

Insult on raske invaliidistav haigus, mis esineb sagedamini vanemaealistel, kuid ligi 25% kõikidest insultidest tekib alla 50-aastastel isikutel (*Bogousslavsky jt. 2003*). Eestis on südame isheemiatõve kui ka peaaju veresoonkonna haiguste suremus oluliselt suurem võrreldes teiste Euroopa Liidu riikidega (*WHO 2001*). Kuna kogu maailmas on tendents keskmise eluea pikenemisele, suureneb ka insuldijuhtude ning sellest tingitud puudega isikute arv ühiskonnas (*Marini jt. 2001*). Vaatamata insuldist põhjustatud koormisele ning selle pidevale suurenemisele, on insuldiga seotud teaduslike uurimuste rahastamine kõikjal lubamatult väikesemahuline (*Pendlebury jt. 2004*).

Rahvastikupõhiste registrite abil on võimalik hinnata haigestumust ja letaalsust, korduvate uuringute põhjal aga nende ajalist muutust konkreetses rahvastikurühmas. Insuldihaigestumuse hindamiseks on vaja registreerida kõik teatud ajaperioodi vältel kindlas piirkonnas tekkivad, tavaliselt esmased insuldijuhud. Registrite koostamiseks on täpsed reeglid (*Sudlow ja Warlow 1996*), mida järgides on võimalik mõõta haigestumust ja letaalsust. Tartu Ülikooli närvikliinikus on insuldi epidemioloogiliste uuringute pikaajalised kogemused: esimene insuldiregister loodi 1970–73 (*Zupping ja Roose 1976*) ning teine aastatel 1991–93 (*Kõrv jt. 1997*). Pikaajaline korduv haigestumuse uurimine annab unikaalset teavet konkreetse haigusega seotud näitajate kohta rahvastikus ning võimaldab analüüsida nende muutumise põhjusi.

Töö eesmärgid

1. Määrata insuldi esmashaigestumus ja 28-päeva letaalsus Tartu rahvastikus aastatel 2001 kuni 2003 ning võrrelda saadud tulemusi teiste rahvastikupõhiste insuldiuuringute andmetega.
2. Analüüsida insuldihaigestumuse ajalisi muutusi Tartus aastatel 1970 kuni 2003.
3. Teha kindlaks transitoorse isheemilise ataki esmashaigestumus Tartu rahvastikus aastatel 2001 kuni 2003 ning võrrelda saadud tulemusi teiste rahvastikupõhiste insuldiuuringute andmetega.
4. Hinnata eluesmase insuldiga patsientide haiglasse jõudmise aega, insuldi riskitegureid ja raskusastet.

5. Teha kindlaks insuldihaigete paranemine ning igapäevaelus toimetulek 6 kuud ja 1 aasta pärast eluesmast insulti ning analüüsida neid mõjutavaid tegureid.
6. Uurida põletiku ning oksüdatiivse stressi markereid veres insuldi ägedas staadiumis ning võrrelda saadud tulemusi tervete kontrollisikute vastavate andmetega (juhtkontrolluuring).
7. Uurida põletiku ja oksüdatiivse stressi mõju insuldist paranemisele.

Patsiendid ja meetodid

Uuringu korraldamisel on kasutatud prospektiivset metoodikat. Registreeritud on nii hospitaliseeritud (TÜK närvikliinik ning teised TÜK osakonnad) kui ka haiglavälised (andmed perearstidelt, lahanguprotokollidest, surmatunnistustelt) esmased insuldijuhud Tartu linna rahvastikus ajavahemikul 01.12.2001 kuni 30.11.2003. Insuldi ja transitoorse ajuisheemia diagnoosid põhinesid Maailma Terviseorganisatsiooni definitsioonidel. Insult on jaotatud alaliikideks, lähtudes kompuutertomograafilise uuringu (KT) tulemustest: isheemiline insult ehk ajuinfarkt (AI), intratserebraalne ehk ajusisene hemorraagia (AH), subarahnoidaalne hemorraagia (SAH) ning klassifitseerimata insult (KI). Isheemilise insuldi alaliigid määrati, lähtudes TOASTi (ingl *Trial of ORG 10172 in Acute Stroke Treatment*) (*Adams jt. 1993*) AI etioloogilise klassifikatsiooni kriteeriumitest: suurte arterite kahjustus, lakunaarne insult, kardioemblooliline insult, teadmata põhjusega insult ning muudest põhjustest tingitud insult.

Registreeriti patsientide demograafilised andmed, kaasuvad haigused, kasutatud ravimid, insuldi raskusaste Skandinaavia insuldiskaala (*Barber jt. 2004*) põhjal ning haiglasse jõudmise aeg. Kaasuvad haigused registreeriti meditsiiniliste dokumentide ja patsientidelt ning nende lähedastelt saadud informatsiooni põhjal.

Insuldihaigete paranemise hindamiseks saadeti patsientidele kuus kuud ning 1 aasta pärast insulti postiga koju küsimustik, mis põhines Bartheli igapäevaeluga toimetuleku skaalal (*Wade ja Langton Hewer 1987*).

Lisaks uuriti insuldi riskitegureid kuni 70-aastastel insuldiga patsientidel ning saadud andmeid võrreldi kontrollisikute tulemustega. Uuritud isikutel määrati vere homotsüsteiini, C-reaktiivse valgu (CRV), fibrinogeeni, kolesterooli ning oksüdeeritud väikse tihedusega lipoproteiini (oxLDL) sisaldus.

Uuringu kiitis heaks Tartu Ülikooli inimuuringute eetikakomitee.

Peamised tulemused

Kaks aastat kestnud uuringu vältel registreeriti kokku 451 esmase insuldiga patsienti keskmise vanusega 71,6 ± 12,3 aastat: 182 meest (40%) keskmise vanusega 67,5 ± 12,3 aastat ning 269 naist (60%) keskmise vanusega 74,3 ± 11,6 aastat.

Haiglaravil viibis 88% patsientidest, pea kompuutertomograafiline uuring tehti 90%-le patsientidest. 40% patsientidest jõudis haiglasse 3 tunni jooksul pärast esmassümptomite teket, 68% jõudis haiglasse 12 tunni ning 82% patsientidest 24 tunni jooksul. Hemorraagilise insuldiga ning raske insuldiga patsiendid jõudsid haiglasse oluliselt kiiremini. Insult oli raskem meestel ning eakatel patsientidel. Kõige raskema sümptomaatikaga olid AH-patsiendid. Isheemilise insuldi alaliikidest olid raskemad kardioemboolne ja suurte arterite kahjustusega insult.

Enamik (82%) esmase insuldiga patsientidest hospitaliseeriti Tartu Ülikooli Kliinikumi närvikliiniku neuroloogia osakonda, 8% andmetest registreeriti perearstide kaudu, 4% erakorralise meditsiini osakonnast, 3% teistest Tartu Ülikooli Kliinikumi osakondadest ning 3% lahanguprotokollidest ja surmatunnistustelt.

AI diagnoositi 332 patsiendil (74%), AH 57-l (13%), SAH 18-l (4%) ning KI 44 (9%) patsiendil. Kõige sagedam AI alaliik, lähtudes TOASTi klassifikatsioonist, oli kardioembooliline insult (35%), järgnesid lakunaarne insult (27%), suurte arterite kahjustus (26%), teadmata etioloogiaga (11%) ning muudest põhjustest tingitud insult (1%). AH ja SAH esinesid valdavalt nooremates vanuserühmades, KI diagnoositi rohkem eakatel (ning peamiselt väljaspool haiglat ravitud) patsientidel. AI alaliikide jaotumisest võib järeldada, et võrreldes teiste rahvastikega esineb Eestis oluliselt rohkem kardioembooliast tingitud isheemilist ajuinsulti. See tulemus viitab asjaolule, et tõenäoliselt on kodade virvendusarütmia ravi antikoagulantidega Eestis olnud puudulik.

Insuldi esmashaigestumus Tartus oli 223 juhtu 100 000 inimese kohta aastas, meestel 203 ning naistel 239. Euroopa standardrahvastiku suhtes vanuse järgi standarditud esmashaigestumus oli 188, meestel 224 ning naistel 164. Kõigis vanuserühmades olid haigestumuskordajad suuremad meestel ning vanuserühmades 55–64 ja 65–74 oli erinevus võrreldes naistega statistiliselt oluline. Saadud tulemuste põhjal võib öelda, et insuldi esmashaigestumus Tartus on võrreldav enamiku Euroopa riikidega ning väiksem kui Norras, Kreekas, Itaalias ja Ukrainas. Samas on aga haigestumus nooremates vanuserühmades suurem kui enamikus võrdlusriikides. Võib öelda, et Eesti mehed haigestuvad insulti 3–8 ning naised 2–6 aastat varem kui nende sookaaslased teistes Euroopa riikides.

Esimese 28 päeva jooksul suri 26% patsientidest (24% meestest ning 28% naistest). Vanuserühmiti naiste ja meeste letaalsuses olulisi erinevusi ei esinenud. Insuldi 28 päeva letaalsus on Tartus suurem kui näiteks Saksamaal,

Itaalias, Norras ning Ukrainas. See võib olla seotud raskema insuldi ja/või halvema tervisliku üldseisundiga Tartu patsientidel.

Insuldi riskiteguritest esines 30%-l patsientidest kodade virvendusarütmia, 61%-l kõrgvererõhktõbi, 14%-l suhkurtõbi, 37%-l südame isheemiatõbi, 6%-l varasem transitoorne ajuisheemia ning 7% patsientidest olid aktiivsed suitsetajad. 8%-l patsientidest ei õnnestunud vaatamata põhjalikele diagnostilistele uuringutele diagnoosida ühtegi insuldi riskitegurit.

Insuldi esmashaigestumus on Tartus viimase aastakümne jooksul oluliselt vähenenud ning saavutanud 1970. aastate taseme. Haigestumuse analüüs näitab, et viimase 10 aasta jooksul on haigestumus vähenenud enamikus vanuserühmades nii meestel kui ka naistel. Oluline haigestumuse vähenemine on ilmne vanuserühmades 45–54, 55–64 ja 75–84 aastat. Kuna esimesed kaks rühma moodustavad tööealised isikud, on muutus kindlasti positiivne. Statistiliselt ebaoluline haigestumuse suurenemine vanuserühmas 65–74 aastat võib olla toimunud seoses haigestumuse vähenemisega nooremates vanuserühmades, mistõttu insulti haigestumine on nihkunud vanemasse earühma. Selle põhjuseks võib oletada tõhusat insuldi ennetustööd, tervislike eluviiside populariseerumist ning südame-veresoonkonnahaiguste riskitegurite paremat käsitlust. Eeltoodud väite tõestuseks on ka fakt, et keskmine vanus haigestumisel on suurenenud, eriti meeste hulgas.

Letaalsusmäära muutused on sarnased esmashaigestumuse trendidega. Üheks letaalsusmäära vähenemise tõenäoliseks põhjuseks on haiglaravile suunatavate patsientide suurenenud osakaal. Insuldihaigete hospitaliseerimise oluline suurenemine Tartus on kindlasti pikaajalise teavitus- ja õpetustöö tulemus. Vaatamata sellele ravib *ca* 8% patsientidest vaid perearst ning 2% sureb enne haiglasse jõudmist.

Üks aasta pärast insulti oli surnud 185 patsienti (65 meest ning 120 naist) ning vastav letaalsusmäär oli 44%. Ühe aasta letaalsusmäär ei sõltunud insuldi alaliigist.

Igapäevaeluga toimetuleku küsimustik saadeti insuldist paranemise hindamiseks ellujäänud insuldihaigetele koju 6 kuud ning 1 aasta pärast insulti. Vastajate osakaal oli vastavalt 82% ja 80%.

Kuue kuu möödudes tuli igapäevaeluga hästi toime (Bartheli indeksi skoor ≥15 punkti, maksimaalne 20) 41% patsientidest ning 1 aasta pärast 36% patsientidest. Regressioonanalüüsi kohaselt soodustasid igapäevaelu toimingutes sõltuvust naissugu, kõrgem vanus, veresuhkru väärtus haigestumisel >10 mmol/l ning raskem insult Skandinaavia insuldiskaala järgi 7. haigestumisjärgsel päeval. Uuritud riskitegurid ning insuldi alaliigid ei mõjustanud igapäevaelus toimetulekut 1 aasta pärast insulti.

Kuni 70-aastaste isheemilise insuldiga patsientide riskitegureid hindava juhtkontrolluuringu tulemused näitasid olulist erinevust homotsüsteiini, triglütseriidide, CRV ja fibrinogeeni, kuid mitte oxLDLi plasmakontsentratsioonides insuldihaigetel võrreldes kontrollisikutega. Suurte arterite ateroskleroosist

tingitud insuldiga patsientidel oli oxLDL sisaldus plasmas oluliselt suurem kui muude isheemilise insuldi alaliikidega patsientidel. CRV suurenenud sisaldus esines 48%-l insuldihaigetest, kuid vaid 4%-l kontrollisikutest. Sarnased olid tulemused ka vere fibrinogeenisisalduse analüüsil: suurenenud väärtused esinesid 39%-l patsientidest ning vaid 1%-l kontrollisikutest. Nii suurenenud CRV kui ka fibrinogeenisisaldus olid seotud insuldi prognoosiga – igapäeva-eluga toimetulek 1 aasta pärast insulti oli nendel patsientidel oluliselt halvem võrreldes haigetega, kelle vastavad väärtused olid normis.

ACKNOWLEDGEMENTS

First of all I would like to thank my family. My mother and father who have supported my studies through long university years and for trusting my choices. Also my spouse Jaan and my son Jan Jürgen for their support and patience during the years of my research.

I would like to express my deepest gratitude to my main supervisor, associate professor Mai Roose, who has outstanding experience in stroke epidemiology, research and practical neurology. Thank you Mai for giving me continuous inspiration and encouragement and for teaching me the basic rules and methods in science.

I would also like to express my deepest gratitude to my second supervisor senior researcher Janika Kõrv for guiding me to science, teaching me to value it and offering the possibility to do research in such an experienced and friendly team.

My warmest thanks to professor Mihkel Zilmer, who has thought me a lot about the molecular mechanisms of vascular diseases and helped to plan and conduct the case-control study of stroke risk factors.

Thanks also to my third supervisor associate professor Sulev Haldre.

My greatest thanks to all my supervisors who always found enough time for long discussions and resolving many problems related to this work despite the difficult situations in their personal life.

I would also like to thank professor Mati Rahu and professor Jaan Eha for a careful revision of my thesis and important suggestions for corrections.

My warmest thanks to the management and whole personnel of the Department of Neurology and Neurosurgery for their help and understanding during the data collection phase.

Special thanks also to doctor Maimu Koort from Gildi Outpatients Clinic, to Ago Kõrgvee for providing the possibility to register patients from hospitals' emergency department and to Milvi Jõeäär in data collection from hospital databases.

I would also like to thank Piibe Muda and Priit Kampus for providing the data, helping to plan and analyse the results of the case-control study.

I would like to thank Svetlana Bizjajeva and Anne Selart for the help in statistical analysis of the data.

I would like to thank Gordon Allan Leman for revising the English of the manuscript and publications.

The study was supported by Estonian Science Foundation research grants 5537 (Janika Kõrv), 6588 (Mihkel Zilmer) and 4342 (Sulev Haldre).

Scandinavian Stroke Scale

Consciousness	**6** – fully conscious
	4 – somnolent
	2 – reacts to verbal command
	0 – coma
Eye movement	**4** – no gaze palsy
	2 – gaze palsy present
	0 – conjugate eye deviation
Arm, motor power	**6** – raises arm with normal strength
	5 – raises arm with reduced strength
	4 – raises arm with flexion in elbow
	2 – can move, but no against gravity
	0 – paralysis
Hand, motor power	**6** – normal strength
	4 – educed strength in full range
	2 – some movement, fingertips do not reach palm
	0 – paralysis
Leg, motor power	**6** – normal strength
	5 – raises straight leg with reduced strength
	4 – raises leg with flexion of knee
	2 – can move, but not against gravity
	0 – paralysis
Orientation	**6** – correct for time, place and person
	4 – two of these
	2 – one of these
	0 – completely disoriented
Speech	**10** – no aphasia
	6 – limited vocabulary or incoherent speech
	3 – more than yes/no, but no longer sentences
	0 – only yes/no or less
Facial palsy	**2** – none/dubious
	0 – present
Gait	**12** – 12m without aids
	9 – walks with aids
	6 – walks with help of another person
	3 – sits without support
	0 – bedridden/wheelchair

MAXIMUM SCORE=58

Modified Rankin Scale

0 No symptoms at all

1 No significant disability despite symptoms; able to carry out all usual duties and activities

2 Slight disability, unable to carry out all previous activities, but able to look after own affairs without assistance

3 Moderate disability, requiring some help, but able to walk without assistance

4 Moderately severe disability, unable to walk without assistance and unable to attend to own bodily needs without assistance

5 Severe disability, bedridden, incontinent and requiring constant nursing care and attention

6 Dead

MAXIMUM SCORE=6 (TOTALLY INDEPENDENT=0)

Barthel Index

1. Bowels	0–incontinent (or needs to be given enemas 1–occasional accident 2–continent
2. Bladder	0–incontinent or catheterized and unable to manage alone 1–occasional accident 2–continent
3. Grooming	0–needs help in personal care 1–independent face/hair/teeth/shaving
4. Toilet use	0–dependent 1–needs some help, but can do something alone 2–independent
5. Feeding	0–unable 1–needs help cutting, spreading butter etc. 2–independent
6. Transfers (bed to chair and back)	0–unable, no sitting balance 1–major help, can sit 2–minor help (verbal or physical) 3–independent
7. Mobility	0–immobile 1–wheelchair independent, including corners 2–walks with help of one person (verbal or physical) 3–independent (but may use any aid)
8. Dressing	0–dependent 1–needs help, but can do about half unaided 2–independent (including buttons, zips etc)
9. Stairs	0–unable 1–needs help 2–independent
10. Bathing	0–dependent 1–independent

MAXIMUM SCORE=20 (TOTALLY INDEPENDENT=20)

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Professional employment

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Special courses

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Study of shaken baby syndrome in Estonia.

2001– University of Tartu, Department of Neurology and Neurosurgery.
Studies of stroke epidemiology and risk factors.
A total of 27 publications, 6 CC articles, 16 presentations in international scientific conferences, 5 publications in Estonian medical journal „Eesti Arst".

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1. **Heidi-Ingrid Maaroos.** The natural course of gastric ulcer in connection with chronic gastritis and *Helicobacter pylori*. Tartu, 1991.
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