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2009

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Citation for published version (APA):

Zia, E. (2009). *The Epidemiology of Intracerebral Haemorrhage. Risk factors and prognosis*. Lund University.

Total number of authors:

1

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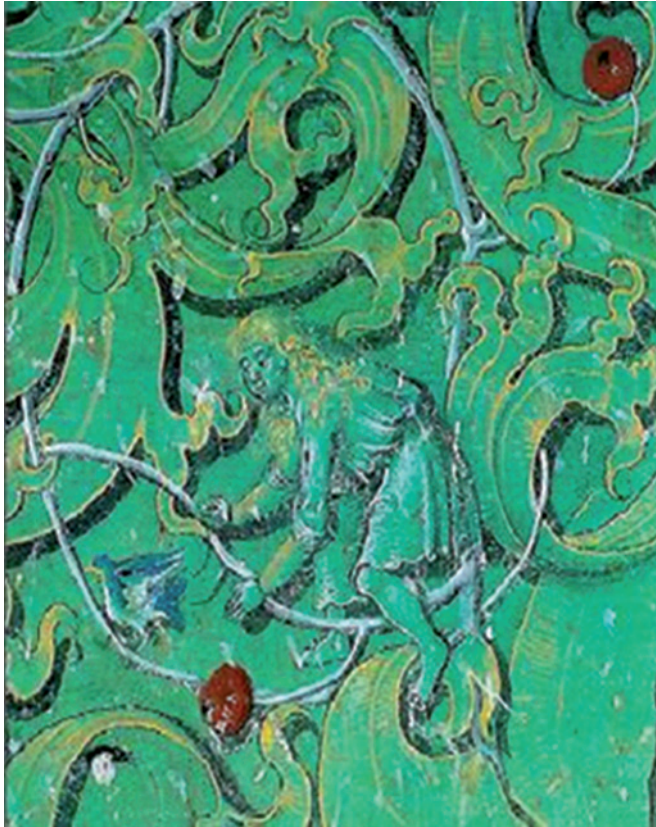
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The Epidemiology of Intracerebral Haemorrhage

Risk Factors and Prognosis

Elisabet Zia

Lund University

The Epidemiology of Intracerebral Haemorrhage

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LUND UNIVERSITY
Faculty of Medicine

2009

Cover: Castel Tasso, Italy. Fresco Murale. Foto postcard, unknown

ISSN 1652-8220

ISBN 978-91-86253-56-1

Lund University, Faculty of Medicine Doctoral Dissertation Series 2009:68

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Printed in Sweden by Media-Tryck, Lund, 2009

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Risk Factors and Prognosis

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LUND UNIVERSITY
Faculty of Medicine

Doctoral dissertation

By due permission of the Faculty of Medicine, Lund University, Sweden,
to be publicly defended in the lecture hall, Department of Obstetrics and Gynecology,
Entrance 74

Malmö University Hospital
Friday October 16 2009, 9.30 am

Faculty Opponent

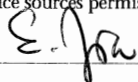
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Organization LUND UNIVERSITY	Document name DOCTORAL DISSERTATION	
	Date of issue October 16, 2009	
	Sponsoring organization	
Author(s) Elisabet Zia		
Title and subtitle The epidemiology of intracerebral haemorrhage. Risk factors and prognosis.		
<p>Abstract</p> <p>The present thesis explored the epidemiology of intracerebral haemorrhage (ICH), i.e., factors associated to incidence and prognosis.</p> <p>In the population of Malmö (Malmö 1990 cohort), it was shown that immigrants from China/Vietnam and the Former Soviet Union had higher risk of ICH than citizens born in Sweden.</p> <p>Although hypertension is a well-known risk factor for stroke, the relation between blood pressure (BP) levels and stroke subtypes is less clear. In the Malmö Diet and Cancer cohort increasing BP was strongly associated with higher incidence of cerebral infarction, as measured by the crude and standardised incidence rates. However, in terms of relative risks (RR), the risk was highest for primary ICH (PICH), especially for nonlobar PICH.</p> <p>The results of previous studies have indicated differences in pathology and genetics between PICH subtypes by bleeding location. In the Malmö Preventive Project cohort, systolic BP and smoking were found to be associated with increased risk of lobar PICH. Systolic BP, psychiatric morbidity and diabetes were found to be associated with nonlobar PICH.</p> <p>Of 474 patients with PICH (Malmö Stroke Registry), 26% died within 28 days and 49% within three years. Male sex predicted 28-day and 3-year mortality, largely explained by high 28-day mortality in male patients older than 75 years.</p> <p>In conclusion, the incidence of ICH varies by country of birth. The impact of high BP, in terms of RR, is highest for nonlobar PICH. Smoking is associated with lobar PICH, and diabetes with nonlobar PICH. Female PICH patients have better survival than men.</p>		
Key words: intracerebral haemorrhage, stroke, stroke subtypes, incidence, prognosis, recurrence, risk factors, prognostic factors, ethnicity, blood pressure, diabetes, smoking, sex		
Classification system and/or index terms (if any):		
Supplementary bibliographical information:		Language English
ISSN and key title: 1652-8220		ISBN 978-91-86253-56-1
Recipient's notes	Number of pages	Price
	Security classification	

Distribution by (name and address)

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SAMMANFATTNING

Enligt siffror från Riks-Stroke (nationellt kvalitetsregister för strokesjukvård), insjuknar ca 30 000 personer i stroke varje år i Sverige. Stroke kan indelas i huvudsakligen tre subtyper; 1) hjärninfarkt (cerebral infarkt), som oftast orsakas av ett eller flera blodkärl i hjärnan täpps till av en blodpropp, 2) hjärnblödning (intracerebralt hematoma), som orsakas av att ett blodkärl i hjärnan brister och leder till blödning i hjärnvävnaden och 3) hjärnhinneblödning (subarachnoidalblödning), där blödningen sker under spindelvävshinnan (arachnoidea). Antalet som insjuknar i stroke varje år, liksom andelen hjärnblödning, skiljer sig åt mellan olika länder och mellan olika etniska grupper.

Hjärnblödning utgör endast ca 10 % av alla stroke, men karakteriseras av dålig prognos. Utöver operation i utvalda fall, saknas det i nuläget effektiva behandlingsalternativ. Endast fyra tidigare större studier från Europa har rapporterat om prognos, och dödligheten efter en månad varierade mellan 31 och 51 %. Kunskap om prognos och prognostiska faktorer har betydelse för främst den enskilde patienten och dennes närstående, men även för planering av vårdinsatser. Det finns, i jämförelse med för t ex hjärninfarkt, förhållandevis få studier som belyser vilka faktorer som är förknippade med ökad risk för hjärnblödning. Förhöjt blodtryck är en välkänd riskfaktor, medan det är oklart om andra påverkbara faktorer som exempelvis diabetes och rökning ger ökad risk för hjärnblödning.

I denna avhandling studeras dels vilka faktorer som har samband med ökad risk för insjuknande i hjärnblödning, dels hur prognosen ser ut efter insjuknande, och vilka faktorer som har betydelse för kort- och långtidsöverlevnad samt återinsjuknande.

Det finns data som tyder på att hjärnblödning är en heterogen grupp, med skillnader i exempelvis genetiska faktorer beroende på blödningslokalisering. Lobär blödning drabbar loberna i storhjärnan och begreppet icke-lobär innefattar blödning i lillhjärnan samt mer djupliggande strukturer (hjärnstam, thalamus och basala ganglierna). Denna uppdelning har använts då vi velat belysa betydelsen av hjärnblödningens lokalisering i olika avseende.

I delarbete 1 fann vi att risken att insjukna i stroke varierade med födelseland. I undersökningen ingick alla registerade invånare i Malmö 1990 i åldrarna 40-89 år (118 134 personer). Under tio års uppföljning, drabbades 6082 av stroke, varav 615 var hjärnblödningar. Jämfört med personer födda i Sverige, hade immigranter från före detta Jugoslavien och Ungern, högre risk att insjukna i stroke (samtliga subtyper), efter att hänsyn tagits för ålder, kön, civilstånd och socioekonomiska faktorer. Risken att insjukna i hjärnblödning var högre hos personer födda i Kina/Vietnam och före detta Sovjetunionen. Den ökade risken för hjärnblödning hos immigranter från Kina/Vietnam överensstämmer med den, i jämförelse med väst, högre frekvensen av hjärnblödning i Asien, vilket delvis anses bero på hög frekvens av högt blodtryck. Från tidigare studier i Malmö vet vi att risken för insjuknande i stroke är högre i stadsdelar

med låg socioekonomisk status. Den ökade risken för hjärnblödning varierar således med födelse-land och tycks kvarstå efter emigration. Det är oklart till vilken grad riskfaktorer för kärlsjukdom (som hypertoni, rökning, diabetes), genetiska faktorer respektive socioekonomiska faktorer bidrar till detta.

Även om högt blodtryck är en välkänd riskfaktor för insjuknande i stroke, är sambandet mellan graden av blodtryck och risken för respektive stroke subtyp inte lika klarlagt. I delarbete 2 ingick deltagare från Malmö Kost Cancer studie (27 702 personer). Under uppföljningstiden (medel 7.5 år) drabbades 701 personer av stroke, varav 88 var hjärnblödning. Vi fann att i absoluta tal var risken att insjukna i hjärninfarkt högre än för hjärnblödning i alla blodtrycksgrupper, vilket är viktigt ur folkhälsoperspektiv. Den relativa risken att insjukna i förhållande till stigande blodtryck, var emellertid högst för hjärnblödning, och främst för icke-lobär hjärnblödning. För denna grupp, var den relativa risken att insjukna 26 gånger större vid blodtrycksvärden på 180/110 mmHg, och däröver, jämfört med blodtryck på 140/90 mmHg. Motsvarande riskökning för hjärninfarkt var 3. Hjärnblödning är, i förhållandevis till hjärninfarkt, ovanligt vid normalt blodtryck vilket kan förklara den med stigande blodtryck branta ökningen för hjärnblödning.

I delarbete 3 fann vi att, utöver förhöjt blodtryck, var diabetes oberoende riskfaktor för icke-lobär hjärnblödning, medan rökning var förknippat med ökad risk för lobär hjärnblödning. Diabetes förekom hos ca 10 % av personerna som drabbades av icke-lobär hjärnblödning, i jämförelse med 2 % vid lobär blödning. Rökning medförde fördubblad risk att drabbas av lobär hjärnblödning. Det är tidigare känt att depression är riskfaktor för stroke, men sambandet mellan depression och hjärnblödning var inte klarlagt. Vi fann att psykiatrisk morbiditet medförde ökad risk att drabbas av icke-lobär hjärnblödning. I studien ingick deltagare från Malmö Förebyggande Medicin studie. Under uppföljningsperioden (medel 14 år), insjuknade 147 personer i hjärnblödning.

I sista delarbetet utvärderades prognosen hos 474 patienter (Malmöbor) som drabbats av hjärnblödning mellan 1993-2000. Vi fann att kvinnor hade bättre kort- och långtidsöverlevnad än män. Skillnaden var mest uttalad hos äldre personer (≥ 75 år). I denna åldersgrupp avled 26 % av kvinnorna inom en månad efter insjuknande, jämfört med 41 % av männen. Efter tre år hade ungefär hälften av patienterna avlidit. Utöver manligt kön, var blödningslokalisering (central och hjärnstam), förekomst av blod i ventriklar, stor blödningsvolym och låg medvetandegrad vid ankomst till sjukhus förenat med ökad risk att avlida. 12 % av patienterna drabbades av en ny stroke inom tre år. Ålder över 65 år var förenat med ökad risk för ny stroke.

Sammanfattningsvis visar dessa studier från Malmö att risken att insjukna i hjärnblödning varierar med födelse-land. Betydelsen av förhöjt blodtryck, avseende relativa risken att insjukna i stroke, är störst för hjärnblödning, och främst med icke-lobär blödningslokalisering. Diabetes har samband med insjuknande i icke-lobär hjärnblödning medan rökning medför ökad risk för lobär hjärnblödning. Kvinnor har bättre överlevnad än män efter hjärnblödning.

ABBREVIATIONS

BMI	Body mass index
BP	Blood pressure
CAA	Cerebral amyloid angiopathy
CI	Confidence interval
CT	Computed tomography
DBP	Diastolic blood pressure
HR	Hazard risk
HT	Hypertensive
ICH	Intracerebral haemorrhage
MDC	Malmö Diet and Cancer
MPP	Malmö Preventive Project
MRI	Magnetic resonance imaging
NT	Normotensive
OAT	Oral anticoagulation treatment
OR	Odds risk
PICH	Primary intracerebral haemorrhage
RLS 85	Reaction level scale 85
RR	Relative risk
SBP	Systolic blood pressure
STROMA	Malmö Stroke Registry
SVD	Small vessel disease
tPA	Tissue plasminogen activator

INTRODUCTION

Stroke – general aspects

Every year, approximately 30 000 people suffer a stroke in Sweden¹. Within one year from stroke onset, 1/3 of the patients die,²⁻⁴ and of the survivors about 10 % will have a second stroke². Globally, there are wide regional differences in stroke incidence⁵. Bearing in mind the large variation between the abilities of different countries to make accurate diagnosis of, and record, strokes,⁶ a recent review showed a 100 % increase of the overall stroke incidence in low-to middle income countries, compared with a 42 % decrement in high-income countries during the last forty years.⁷

According to the definition established by the World Health Organisation, stroke is rapidly developed clinical signs of focal or global deficits of cerebral function, lasting more than 24 hours, or until death, with no apparent non-vascular cause⁸. In practice, stroke is a heterogeneous disorder consisting of three types which differ in risk profiles, management and prognosis.⁹⁻¹¹

The three types are 1) cerebral infarction (or called ischemic stroke), mostly caused by an occlusion of a cerebral vessel, 2) intracerebral haemorrhage (ICH), caused by a ruptured cerebral vessel and bleeding into the cerebral parenchyma, and 3) subarachnoidal haemorrhage, a bleeding into the subarachnoidal space. ICH and subarachnoidal haemorrhage are together sometimes mentioned as haemorrhagic stroke, however these subtypes differ in vasculopathy,¹² incidence,^{13, 14} risk factors¹⁵ and prognosis,¹² and they are usually differentiated in epidemiological studies.

In western communities, cerebral infarction accounts for approximately 75 % of all stroke events¹⁶⁻²³ and is associated with overall better survival than the other types.¹¹ Cerebral infarction is also the most studied subtype in terms of risk factors, prognosis, and management,^{11, 24} which has contributed to land breaking treatment possibilities.^{25, 26} Of the clinically verified stroke cases, 5-10 % do not undergo the diagnostic procedures for sub-classification. Subarachnoidal haemorrhage accounts for ≈ 5 % and ICH for the remaining 10 %.¹⁶⁻²³

Epidemiology [Gr. *epidēmios* prevalent], is the science concerned with the study of the factors determining and influencing the frequency and distribution of a disease, injury and other health-related events and their causes in a defined human population.²⁷ This thesis has focus on risk factors and prognosis of ICH in the city of Malmö, Sweden, even though the other stroke subtypes are discussed and handled in some aspects.

Intracerebral haemorrhage

Definition and types

Spontaneous ICH is a bleeding into the brain parenchyma without trauma or surgery. If the vessel rupture in ICH occurs close to the cortical surface, or deep in the hemisphere, an associated bleeding into the subarachnoid space and brain ventricles may arise. Spontaneous ICH may be divided into primary respectively secondary haemorrhages, depending on the underlying cause of the bleeding. However, the terminology varies considerably, and the usage of 'spontaneous ICH' equivalent to 'primary ICH' is not uncommon.

Primary intracerebral haemorrhage (PICH) accounts for ~80% of all ICH. In general, PICH is considered when the bleeding occurs *without* provocation of trauma or a number of anatomical, haemodynamic, pharmacological and hemostatic factors related to secondary intracerebral haemorrhage. Nevertheless, there are wide variations in to what extent the investigators exclude cases with these provoking factors in epidemiological studies. Warfarin treatment is often included as a possible risk factor or predictor of outcome after PICH, and the case-exclusion procedures is mostly restricted to haemorrhages related to vascular malformations, aneurysm, tumor, tPA treatment, and cerebral infarction. These latter criteria were applied in defining PICH in this thesis.

PICH vascular pathology

Two main vascular pathologies have been identified in association to PICH; cerebral amyloid angiopathy and small vessel disease. In sporadic cerebral amyloid angiopathy (CAA) there is an infiltration by β -amyloid protein in the vessel wall of small and medium-sized predominantly cortical and leptomeningal blood vessels, which induce vessel wall fragility and risk of rupture.^{28, 29} In consecutive autopsies the prevalence of CAA was 23-49% and increased with age.²⁹⁻³¹ An association to intracerebral haemorrhage was first described in the 1960s.³² Bleeding from the cortical and leptomeningal vessels give rise to so called **lobar haemorrhage** localised in the cerebral cortex or subcortical white matter substance.²⁸ CAA as verified by autopsy has later been observed in 11-49 % of cases with intracerebral haemorrhage.^{30, 33-35} In ICH cases with hypertension, CAA-lesions were never found in the basal ganglia region, rarely in the cerebellum and most frequent in the occipital and frontoparietal cerebral lobes.³⁴

A correlation has been found between apolipoprotein E polymorphism $\epsilon 4$ ³³ respectively $\epsilon 2$ ³⁶ and ICH related to CAA ($\epsilon 3$ is the 'normal' genotype). These studies were performed on North American populations, and in an European study, no such association was found.³⁷ Definite diagnosis of cerebral amyloid angiopathy require neuropathologic examination, however clinical diagnosis of possible respectively probable CAA-related ICH according to the Boston Criteria^{33, 38} has high accuracy.³⁹

Small vessel disease (SVD) comprise a numerous of different vasculopathies.^{40, 41} SVD-related haemorrhages arise in particular from the perforating arterioles, terminal

vessels, which supply the basal ganglia, thalamus, brainstem and the cerebellum. Vessel rupture in these brain locations gives rise to **non-lobar haemorrhages**. Rupture mostly occurs at distal vessel bifurcation sites⁴². Lipohyalinosis, or ‘complex small vessel disease’⁴³ was first described in association to lacunar infarction,⁴⁴ and later in relation to ICH.⁴⁵ Lipohyalinosis is characterised by loss of the normal vessel wall architecture (segmental wall thickening and thinning), collagenous sclerosis and mural foam cell infiltration,⁴⁴ and in its acute form, so called fibrinoid necrosis.^{43, 46-48} Most of the pathological studies included exclusively ICH-cases with hypertension.^{34, 42, 45-47} In a later conducted autopsy study, which included both normo- and hypertensive cases of SVD in association to various cerebral conditions, including ICH,⁴⁹ lipohyalinosis or fibrinoid necrosis were rarely observed. Instead, the small-vessel morphology, which was identical in normo- and hypertensive cases, corresponded to the so called hyaline arteriolosclerosis, or ‘simple small vessel disease’.⁴³ In arteriolosclerosis, the smooth muscle cells first hypertrophies, and then are replaced by fibroblasts and deposits of collagens, resulting in a homogenous vessel wall thickening, and lumen narrowing.⁵⁰ Arteriolosclerosis appears in various degrees with increasing age.⁵¹ It was suggested that the nature of cerebral SVD have changed since the original description⁴⁴ as a consequence of diminished proportion of SVD related to hypertension.⁴⁹

The vascular pathology in lobar respectively nonlobar PICH may still not be as distinct as described above. In CAA-related bleedings, 84 % were lobar and 16 % nonlobar bleeding location.³⁰ The major histological difference between cases with CAA-related lobar haemorrhage, and cases who had CAA *without* haemorrhage, was the co-presence of SVD in cases with haemorrhage.⁵² Additionally, CAA- affected vessels was suggested to indirectly induce nonlobar PICH, by impairment of the auto-regulation.³⁴ However, in one study, the vessel wall of cortical branches had normal histological appearance in cases with hypertension and non-lobar ICH attributed to lipohyalinosis.⁴²

In summary, both CAA and SVD were observed in lobar PICH, whereas mainly SVD seems related to nonlobar PICH. However, pathological studies on PICH are rare, and none included unselected cases.

Incidence and risk factors

Demographic aspects

The age-standardised annual incidence of PICH per 100 000 person-years has been estimated to 28-33 in Europe,^{14, 53} versus for example 47 in Japan.⁵⁴ The incidence of PICH is higher among men than women, and increases with age.⁵⁵ Population-based western studies show both stable^{56, 57} and decreasing^{4, 23} ICH incidence in the last decades. However, worldwide, in low-to middle-income countries, the current age-adjusted incidence rate of ICH and the frequency of ICH as stroke subtype, have been reported to be almost twice those reported in high-income countries.⁵⁸

Ethnicity appears to influence on the incidence of ICH regardless of the country of residence. The incidence of ICH is twice among African Americans in USA^{59,60} and Asians in New Zealand⁶¹, as that among Whites in the respective populations. The distribution of stroke subtypes also differs between patients with different ethnic origin. Out of all stroke, approximately 20 % are ICH in populations with Asian,⁶¹⁻⁶⁴ Black⁶⁵⁻⁶⁸ and Hispanic^{66,69,70} ethnicity, compared with 10 % in White populations.¹⁶⁻²² Non-lobar PICH is also more common in Black^{59,71} and Hispanic⁷¹ patients than in White patients. However, it should be borne in mind that comparison of ICH incidence and stroke subtype ratios between populations in different countries is complicated by differences in methodological and diagnostic procedures⁷. Only a few studies have included multiple comparative ethnic subgroups within the same local study population.^{61,66}

Blood pressure

Elevated blood pressure is a well established risk factor for the incidence of both PICH and cerebral infarction,^{55,72} and there is a linear relationship between the increment of blood pressure value and the relative risk of stroke.⁷³ In a Korean study, the relationship with increasing blood pressure was found to be stronger for PICH than for ischemic stroke,⁷⁴ however it is not known whether this is also true in Western populations. The term ‘hypertensive haemorrhages’ has been used to describe PICH with nonlobar location,⁴⁵ and mainly derives from the fact that autopsy studies at the time were mostly carried out on cases with hypertension and a high rate of the haemorrhages were nonlobar. Although the importance of hypertension in lobar bleeding has been demonstrated⁷⁵, results on the relation between hypertension and PICH subtypes in case-control studies are inconsistent⁷⁶.

Metabolic risk factors

In those aged 35-74, individuals with diabetes have been found to have five (men) to eight (women) times higher risk of stroke than non-diabetics.⁷⁷ The association to cerebral infarction is well known^{72,78-80} whereas the relationship between diabetes and PICH is less clear. Diabetes has been found to be a risk factor for PICH in young patients⁸¹ and in men,⁷² However, in a recent meta-analysis of 8 case-control studies⁵⁵ diabetes was not a risk factor for PICH and it has been suggested that diabetes is inversely related to PICH.⁸²

Elevated total cholesterol levels are positively related to an increased risk of cerebral infarction,⁸³⁻⁸⁶ in particular atherosclerosis- and small vessel disease,⁸⁷ but the results are inconsistent.¹¹ The relationship between cholesterol and the risk of PICH seems to be inverse^{72,87-91} or u-shaped.⁸⁵ Other reported no association^{92,93} or only in elderly men.⁹⁴ Low cholesterol values seem more common in cases with nonlobar haemorrhages, compared with cases with lobar haemorrhages⁹⁰. Some biological explanations of why lower cholesterol levels could induce PICH are weakening of the endothelial wall due to smooth muscle cell necrosis,⁴⁷ reduction of platelet aggregability⁹⁵ and increase in the osmotic fragility of the erythrocyte cell

membrane.^{96,97} An indirect relation, for example when low cholesterol levels are primary related to other disorders, as chronic liver disease, has also been suggested.⁹⁸ Elevated non-fasting triglycerides levels^{85,99} and body mass index (BMI),¹⁰⁰⁻¹⁰³ have been found to be associated with an increased risk of cerebral infarction, whereas the relationship to haemorrhagic stroke appear to be inconsistent for both triglycerides^{85,88,104} and BMI.¹⁰⁰⁻¹⁰³

Smoking

Some have found no association between smoking and PICH¹⁰⁴⁻¹⁰⁷ while others have found positive relations,^{72,108-110} in contrast to cerebral infarction, in particular the subtype related to large vessel atherosclerosis.¹⁰ It is not known if smoking has different impact on lobar respectively nonlobar PICH.

Alcohol

An increasing risk of PICH with ‘moderate’^{55,72,111} to ‘heavy’ alcohol-intake,^{55,112} as compared with non-drinkers, have been reported, taking into accounts differences in cut off points of alcohol consumption between the studies. However, one study showed no association¹⁰⁴ and another only to lobar PICH.¹⁰⁷ Some potential mechanisms by which alcohol could provoke PICH are a) enhancement of hypertension b) direct vasoconstriction and increased intracellular calcium-levels, inducing endothelial damage and c) haematological effects as thrombocytopenia and decreased platelet aggregation.¹¹³

Depressive disorder

Depression is commonly diagnosed *after* stroke,¹¹⁴ but it is difficult to establish whether the depression also pre-dated the stroke. Cerebrovascular lesions (without clinical signs of stroke) on brain images are related to the development of depressive symptoms over time.¹¹⁵ On the other hand, individuals with depressive symptoms have an increased risk of suffering a cerebral infarction later on.¹¹⁶⁻¹¹⁹ Both behavioural and vascular risk factors^{120,121} as well as vascular impairment¹²² may explain this increased stroke risk. In one study, the association was restricted to fatal stroke, suggesting that psychological distress could be associated with more severe strokes, or that the patients recovery potential might have been impaired by psychological problems and/or comorbidities (i e cardiac or other severe illnesses).¹¹⁷ It is not known whether there is any relation between psychological distress and PICH.

Socioeconomic circumstances

Groups with low socioeconomic status, as measured by levels of education and/or occupation, income, profession, migration rate or dependency of social welfare support,¹²³⁻¹²⁶ have an increased risk of stroke overall, as well as ICH.¹²⁷ A higher prevalence of vascular risk factors (for example hypertension, diabetes and smoking) in groups with low socioeconomic status, partly explains this relationship.^{124,126}

However adjustment for vascular, lifestyle or psychosocial risk factors did not change the relationship between stroke and socioeconomic status.¹²⁵

Σ

Hypothetically, relating to potential differences in vascular pathology, the above mentioned risk factors might have different impact on the incidence of lobar respectively nonlobar PICH. To the best of our knowledge, no prospective study with pre-event established risk factors, has reported on risk factors of PICH subtypes.

Prognosis

Recent studies have reported considerable variation in outcome after ICH, with one-month case fatality rates between 13 and 51 %, ^{18, 53, 54, 128-132} the lowest rates being found in Japan.^{54, 132} After one year 47-61 % of the patients had died ^{18, 53, 128-130, 133, 134}, after three year 52 % ¹⁸ and after 10 year 76 %.⁵³ Only two of these studies concerned the survival of patients treated in a single hospital,^{18, 131} the others included patients from multiple centres.^{53, 54, 128, 130, 132-134} Considering the number of patients included in the respective study and the length of the study period, this means that each centre handled few PICH-cases, which may have had a negative impact on outcome.¹³⁵

Risk factors for mortality

Age and sex

Increasing age is a well established predictor of high mortality following PICH ¹³⁶. The mean age at the time of stroke is higher in women than men,¹³⁷ Whether the age-corrected mortality rates are different for men and women with PICH is unclear. It has been reported that older men had higher one-month age-adjusted mortality after stroke overall, as compared to women,^{138, 139} but the results are not consistent. ^{18, 140, 141} Few studies reported on mortality rates after PICH in men and women separately.^{128-130, 142} Male sex was found to be an independent risk factor for long-term mortality in patients who survived the first month after PICH.¹²⁹ A different study showed a higher mortality rate in women, but after adjustment for other risk factors, female sex was not a predictive factor for death.¹³⁰

Haemorrhagic characteristics

Already twenty years ago, it was shown that one month mortality rates depended highly on the brain damage caused by the haemorrhage, i.e. on the haemorrhage volume and extension of the haemorrhage to the cerebral ventricles.^{143, 144}

Intraventricular haemorrhage is most common in haemorrhage in the thalamus, nucleus caudatus and cerebellum.⁵⁴ Haemorrhage volume and intraventricular haemorrhage, together with age and the clinical condition of the patient on admission, as measured by level of consciousness, are the main items in prognostic grading scales.^{145, 146} However, few studies with unselected PICH cases have verified the

impact on mortality, after adjustment for all these factors, as well as other potential predictors, for example haemorrhage site,^{54, 130, 147} and the results are inconsistent. In 20-40% of the ICH events, the haemorrhage volume expands during the first hours after onset^{148, 149} and this volume growth is independently related to the baseline volume^{150, 151} and higher mortality.¹⁵¹ The relationship between haemorrhage volume and outcome varies by haemorrhage location, with less difference in lethal versus non-lethal volume in cerebellar and brainstem haemorrhages, as compared to lobar respectively central haemorrhages.^{54, 147} Brainstem haemorrhage has the highest one-month case fatality rate, 53-80%,^{54, 128, 130} while the corresponding rate in lobar haemorrhage is 11-46%.^{54, 128, 130}

Oral anticoagulation treatment

At the University Hospital in Malmö, the three most common indications for OAT are atrial fibrillation, venous thromboembolism and mechanical valve prosthesis. Patients with oral anticoagulation treatment (OAT) have approximately 10 times higher risk of intracerebral haemorrhage as compared with the general population.¹⁵² One-month fatality in OAT-related haemorrhages in unselected groups has been reported to be 44-55%.^{130, 131, 152, 153} Although those receiving OAT showed significantly higher one-month fatality than those without treatment, OAT was not independently related to short-term mortality after adjustment for haematoma volume.¹³⁰ The results of studies on whether OAT is associated with larger baseline haemorrhage volume are inconsistent,^{154, 155} but haematoma expansion in the acute phase seems to be more pronounced in patients on OAT, independent of baseline volume.^{154, 155} The studies described included patients with previous stroke, and the impact of OAT on mortality in unselected first-ever PICH is unknown.

Management and outcome

There are several modifiable factors associated with increased mortality in patients with PICH. High blood pressure predispose for enlargement of the bleeding^{156, 157} which might explain why elevated blood pressure on admission is a predictor of short term mortality, independently of the presence of hypertension prior PICH event¹⁵⁸. In 45 330 patients admitted to emergency departments, 75 % had systolic blood pressure (SBP) > 140 mmHg.¹⁵⁹ It was reported that enlargement occurs in 9 % of the patients with blood pressure target of SBP ≤ 150 mmHg, versus 30 % in patients with SBP ≤ 160 mmHg,¹⁵⁷ and pharmacological treatment of high blood pressure (SBP 150-220 mmHg) in the acute phase with blood pressure target of SBP 140 mmHg seems to be related to decreased haemorrhage growth.¹⁶⁰

High blood glucose on admission seems to be associated with more severe bleeding.^{158, 161} However, if it is related to early death, independently of diabetes, is not clear.^{158, 161} In approximately 50 % of the cases with haemorrhagic stroke some abnormality on ECG is observed in the first 24 hours. Sinus tachycardia, ST-depression and inverted T-waves predicted increased three month mortality, independent of age, stroke severity and pre-stroke handicap.¹⁶² These specific changes are believed to be related to the stroke per se, as opposed to for example atrial

fibrillation which is a sign of a manifest cardiac disease. It is, however, not known if pharmacological treatment of the tachycardia would improve outcome.

According to the recommendations of the American Heart Association/American Stroke Council from 2007, patients with cerebellar haemorrhage > 3 cm with neurological deterioration or who have brain stem compression and/or hydrocephalus from ventricular obstruction, should have surgical removal of the haemorrhage. In addition, patient with lobar haemorrhage within 1 cm of the brain surface, might be considered for surgical evacuation by standard craniotomy (as opposed to other surgical techniques).¹⁶³ However, the surgical frequency varies largely between centres. For example, in some hospitals in Japan⁵⁴ the surgical frequency was 36 % as compared with 10 % in the USA.¹²⁸

Care in acute stroke unit improves short-term survival after stroke,¹⁶⁴ including PICH.^{165, 166} Although there probably are large differences in local praxis, assessment in intensive-care units is not uncommon. It has been estimated that approximately 30 % of patients with supratentorial haemorrhage and almost all patients with brainstem or cerebellar haemorrhage, require intubation in the acute phase.¹⁶⁷ In severely ill patients, do-not-resuscitate orders (DNR) may be appropriate. A DNR indicates that no resuscitation should be attempted in case of cardiopulmonary arrest. It was shown, however, that DNR not only have implications in case of cardiopulmonary arrest. Hospitals with high rate of early DNR in patients with ICH, also had lower rates of aggressive management and treatment of the disease, and these hospitals also had higher in-hospital mortality after ICH.¹⁶⁸

Recurrence rate

In a review of hospital- and community based studies, the recurrence rates from pooled data were 4 and 6 % per patient-year, respectively. Approximately half of the recurrent events were haemorrhagic.¹⁶⁹ In the same review, recurrence was more frequent among cases with lobar PICH as first event. In lobar ICH, apolipoprotein E polymorphism $\epsilon 4$ and $\epsilon 2$ are predictors for recurrent haemorrhage.¹⁷⁰ Two main patterns have been described, with respect to the relationship of the first and the recurrent haemorrhage; ganglionic-ganglionic and lobar-lobar, where the first pattern is more common in Asia^{171, 172} and the second in Europe.¹⁷³⁻¹⁷⁵ In persons with former stroke (within five years) a blood pressure reduction of an average of 9,0/4,9 mmHg (systolic/diastolic BP) with antihypertensive treatment reduced the stroke recurrence risk by approximately 30 %. The risk reduction was highest for those with previous ICH as stroke subtype.¹⁷⁶ Although the value of antihypertensive treatment after stroke is well-established, the knowledge of specific secondary prevention strategies after PICH is limited.

AIMS

1. To investigate the incidence of stroke subtypes in relation to country of birth (paper I)
2. To explore the relationship between blood pressure and the incidence of cerebral infarction, PICH and PICH with lobar and nonlobar location (paper II)
3. To investigate the impact of vascular and environmental factors on the risk of PICH and PICH with lobar and nonlobar location (paper III)
4. To investigate the survival and stroke recurrence after PICH in relation to demographic, clinical and haemorrhagic characteristics (paper IV)

SUBJECTS AND METHODS

General introduction- an overview of the methods employed in each study

Paper I Prospective cohort study

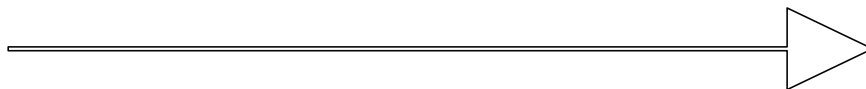
Malmö 1990 cohort

screening

1990

incidence of stroke

until dec 31, 2000



Paper II Prospective cohort study

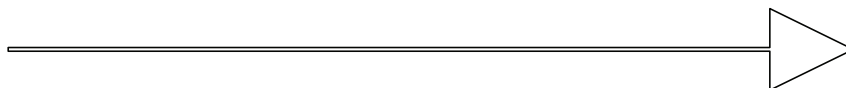
Malmö Diet and Cancer cohort

screening

1991-1996

**incidence of
cerebral infarction and PICH**

until dec 31, 2001



Paper III Nested case-control study

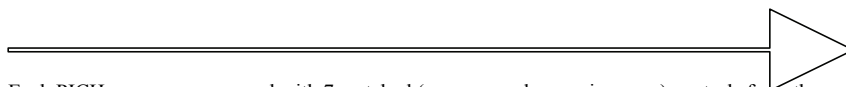
Malmö Preventive Project cohort

screening

1974-1992

incidence of PICH

until dec 31, 1999



Each PICH case was compared with 7 matched (age, sex and screening-year) controls from the same cohort.

Paper IV Prospective cohort study of PICH patients

Malmö Stroke Register PICH cohort

PICH event

1993-2000

incidence of death and recurrent stroke

within 3 years



Study populations

Paper I

Malmö 1990

This population-based cohort consists of all Malmö residents between 40 and 89 years of age, according to the Population Census Data from 1990,¹⁷⁷ in total 118 134 individuals (52 877 men and 65 257 women). The register included information on country of birth, marital status, type of housing (rented and owned), and annual income, based on information from a mailed questionnaire (response rate 97.5%) and data from other population registers. Only immigrants from countries with total follow-up times of $\approx >2500$ person years were included in the analysis. Participants with missing information on birth country (n=51, 0.04 %) were excluded. In total 113 662 persons were included in this study, of whom 98 961 were born in Sweden and 14 701 in other countries.

Paper II

The Malmö Diet and Cancer study

The Malmö Diet and Cancer study (MDC) is a prospective population-based study, with the main objective of evaluating diet-related risk factors for cancer.¹⁷⁸ However, the investigation also included a number of items related to cardio- and cerebrovascular diseases. All men born between 1923-1945 and all women born between 1923 and 1950, residing in Malmö in 1991 (n=74 138), were invited by letter or through newspaper advertisement to participate in the study. Reading and writing skills in the Swedish language were criteria for eligibility. 1 975 persons were excluded due to language problems or mental incapacity, and 3 258 persons died or moved out before completing the baseline examination. In all, 28 449 persons participated, out of an eligible population of 68 905 persons (participation rate 40.6 %)¹⁷⁹.

Baseline examinations were undertaken between 1991 and 1996. The participants were first invited to a screening centre at Malmö University Hospital, where they were asked to fill in a written paper-questionnaire covering socioeconomic, demographic and lifestyle factors as well as information on previous and current diseases and medication, and diseases among relatives, in total 141 questions. Research nurses conducted various measurements including blood pressure, height and weight, and collected assorted blood samples. On a second visit occasion, individual interviews regarding detailed diet history were performed by trained dietary interviewers. In our study, those reporting a previous stroke at screening (n=324), and those for which information on blood pressure (n=44), BMI (n=46), smoking (n=324) and/or alcohol consumption (n=323) was lacking were excluded from the present study, resulting in a cohort of 27 702 subjects.

Paper III

Malmö Preventive Project

The Malmö Preventive Project (MPP) was organised and carried out by the Department of Medicine at the Malmö University Hospital, with the aim of identifying individuals at high risk of cardio- and cerebrovascular diseases in a population-based cohort.¹⁸⁰ Complete birth cohorts (1921, 1926-1942, 1944, 1946, 1948-1949 for men and 1926, 1928, 1930, 1932-1936, 1938, 1941-42, 1949 for women) of registered residents of the city of Malmö were invited by letter to a health examination. The participation rate was 71%, and in total 22 444 men and 10 902 women participated. Their age ranged from 27 to 61, and the mean age was 47 years. The screening program, performed at Malmö university hospital between 1974 and 1992 (1974-1983 for men and 1976-1992 for women), comprised a physical examination, a panel of laboratory tests and a computerised self-administered questionnaire. Subjects in whom diseases or risk factors were detected at screening (~30%) were referred to the appropriate clinic for medical care and further evaluation and/or intervention. Subjects reporting myocardial infarction or stroke before the baseline examination were excluded from the present study (n=341).

Paper IV

Malmö Stroke Register PICH cohort

This patient cohort includes all cases of PICH (n=474), as described below, registered in the Malmö Stroke Register (STROMA) between January 1, 1993 and December 31, 2000.

Case retrieval

Paper I-IV

Malmö Stroke Register - STROMA

The STROMA register contains information on cases of stroke since 1989¹⁸¹ both first and recurrent stroke events according to the same case ascertainment procedure. Recurrent stroke cases are registered in a separate recurrence register if first ever stroke occurred before 1989. Only stroke cases in Malmö residents are included in STROMA. Case identification is carried out by a specialised research nurse, and consists of a continuous broad search among patients admitted to the emergency and admission department, the neurological wards and ambulatory department, as well as other relevant hospital wards, for neurological symptoms and diagnosis that could indicate stroke. Patients initially hospitalised for other initially reasons, are also included in the case identification procedure. All possible stroke cases were validated by reviewing the patients' records under the supervision of a senior stroke physician.

Malmö University Hospital is the only hospital serving the population of Malmö. Primary care and nursing homes work in collaboration with the University Hospital, and patients with symptoms of stroke at those healthcare facilities are routinely referred to the hospital for further examination and are thus included in the case identification process. The WHO's definition of stroke is used.⁸ In the database, stroke subtypes are coded according to ICD 9 (434, 430, 431 and 436).¹⁸²

Other sources of case retrieval

The National Patient register 183 was used to find cases among the participants in the MPP and MDC' cohorts who moved out from the city of Malmö during the follow-up period (paper II and III). The Swedish Causes of Death register 184 was used to provide information of death and cause of death (paper I-IV). In this case search procedure, International Classification of diseases (ICD) revision 9 and 10182 was used, ie 434.0-9 / I63.0-9 for cerebral infarction, 431.0-9 / I61.0-9 for intracerebral haemorrhage, 430.0-9 / I60.0-9 for subarachnoidal haemorrhage and 436.0-9 / I64.0-9 for unspecified stroke, according to the established endpoints in the respective studies. In paper II-IV, cases with ICD codes indicating ICH or undefined stroke underwent the same diagnosis validation procedures as for STROMA. In paper III (MPP), cases with ICH and undefined stroke before 1989 were retrieved from the national registers and the recurrence register in STROMA.

Ascertainment of PICH diagnosis, classification and haemorrhage characteristics

Intracerebral haemorrhage was diagnosed when CT, MRI, or autopsy showed intraparenchymal blood in the brain. Angiography was carried out in selected cases with haemorrhagic stroke, i.e., when haemorrhage location, age or clinical status was suggestive of a vascular malformation. In all verified cases of intracerebral haemorrhage, the CT images were reviewed with the assistance of a neuroradiologist (Dr. Toivo Matilainen), with regard to haemorrhage volume, the presence of intraventricular haemorrhage, and the location of the haemorrhage. Cases were excluded if the haemorrhage was considered to be secondary (e.g. caused by arteriovenous malformation/aneurysm, thrombolysis of acute myocardial infarction, haemorrhagic infarction or tumor).

Haemorrhage location was classified into four regions; lobar (predominantly cortical or subcortical white matter), central (predominantly basal ganglia, internal capsule, periventricular white matter), cerebellum and brainstem. In the studies described in paper II and III, central, brainstem and cerebellar locations were categorised as one PICH subtype (nonlobar), whereas in the study presented in paper IV, they were analysed separately. The volume of the haemorrhage was calculated using the formula $AxBxC/2$.¹⁸⁵ Intraventricular haemorrhage was assessed as present or absent.

Assessment and definition of risk factors

Paper I (Malmö 1990)

Country of birth

The participants in the Malmö 90 cohort provided information on their country of birth in a self-administered questionnaire. This information was lacking for 51 participants (0.04%) in the Malmö 90 cohort. Only immigrants from countries with total follow-up times of ≥ 2500 person years were included in the analysis.

Marital and Socioeconomic status

The total income in 1990 of each individual, was divided into six categories: 0-49 000, 50 000-99 000, 100 000-149 000, 150 000-199 000, 200 000-249 000 and $\geq 250 000$ Swedish crowns (SEK) per year (1 USD \approx 6 in 1SEK in 1990). Information on housing, tenant or house-owner, was included in the assessment of socioeconomic status. Marital status was assessed as married or unmarried.

Paper II (MCD)

Blood pressure

Blood pressure was measured twice, with a mercury sphygmomanometer, in the right arm after a 10 minutes rest and the average value was used. The blood pressure values were grouped according to the guidelines of the European Society of Hypertension and European Society of Cardiology from 2003,¹⁸⁶ i.e. $<140/<90$ mmHg (normal blood pressure), systolic blood pressure (SBP) 140-159 and/or diastolic blood pressure (DBP) 90-99 mmHg, SBP 160-179 and/or DBP 100-109 mmHg and SBP ≥ 180 and/or DBP ≥ 110 mmHg as hypertension grades I-III, respectively.

Metabolic factors

Diabetes was defined as having anti-diabetic medication (both insulin and non-insulin) or self-reported diabetes according to questionnaire. Hyperlipidemia was defined as use of lipid-lowering drug treatment. Weight was measured to the nearest kilogram using balance-beam scale with subjects wearing light clothing and no shoes. Height was measured with a fix stadiometer calibrated in centimetres. Body mass index (BMI) was calculated as $\text{weight}/\text{height}^2$, and assessed in kg/m^2 .

Smoking and drinking habits

Smoking was defined as current smoking, daily or regularly. High alcohol consumption was defined as > 40 g/ day for men and > 30 g/ day for women,¹⁸⁷ according to the consumption reported in the menu book.

Paper III (MPP)

Blood pressure

Blood pressure was measured as described above for the MDC.

Hypertension was defined as having blood pressure $\geq 160/95$ mmHg and/or treatment for hypertension.

Metabolic factors

Blood samples for analysis of blood glucose, serum total cholesterol and triglycerides were taken after an overnight fast, and analyzed as non-frozen samples at the department of clinical chemistry at Malmö University Hospital.

Diabetes was defined as fasting whole blood glucose ≥ 6.7 mmol/l, according to the World Health Organization definition from 1980,¹⁸⁸ or self-reported diabetes according to the questionnaire. Weight and height was measured in the same manner as in the MCDS (see above).

Life-style related factors

Smoking was defined as current smoker, according to the questionnaire. Alcohol abuse was defined as having a history of problematic alcohol behaviour according to the questionnaire, or by means of the results according to the modified shortened version of the Michigan Alcoholism Screening Test.¹⁸⁹ This test included nine questions (included in the MPP questionnaire), and subjects with more two or more affirmative answers were considered to be high-consumers of alcohol.

Subjects who reported that they were mostly engaged in sedentary activities in their spare time, for example with watching TV, reading or going to cinema, were categorised as physically inactive. Information about cohabiting status, defined as living without partner or not, was retrieved from The National Swedish Censuses investigations in 1975, 1980, 1985 and 1990.¹⁷⁷ Information from the year closest to the year of the participant's screening year was used.

Psychiatric morbidity

History of psychiatric morbidity was based on the responses to the question '*Have you ever received treatment or care for nervous or psychiatric problems, ?*', Yes or No.

Paper IV (Malmö Stroke Register PICH cohort)

Vascular risk factors

Data on vascular risk factors at the time of PICH were retrieved from the patient records. Data were collected on the following risk factors; ischemic heart disease (i.e. history of angina pectoris and/or cardiac infarction), treatment for hypertension, current or former smoking, and diabetes mellitus (previously known or newly diagnosed). Hypertension, smoking and diabetes were defined according to the corresponding items registered in the Swedish Stroke Register.¹⁹⁰

Data on vascular risk factors was missing as follow; treatment for hypertension n=79, smoking n=191, ischemic heart disease n=77 and diabetes n=83. These were coded in a separate category, in order not to lose them in the multivariate models.

Oral anticoagulation treatment

Information on oral anticoagulation treatment (OAT), i.e. warfarin treatment, at the time of PICH, was collected from the patient records and from the patient register at the Anticoagulation Clinic at Malmö University Hospital.

Level of consciousness

The level of consciousness on admission to the hospital was assessed according to the Reaction Level Scale (RLS 85).¹⁹¹ This is an eight graded scale. Data were collected from the patients' records and the RLS scores were categorised into three groups; 1 (alert), 2-3 (drowsy) and 4-8 (unconscious). Information was not available in 5 cases.

Statistical methods

The expected number of stroke cases in the immigrants groups was calculated by standardisation for age (5-year groups) and sex using the indirect method. Cox proportional hazards model was used to compare incidence rates with adjustments for age, sex, marital status and socioeconomic indicators (Paper I).

In paper II, the incidence (per 1000 person-years, py) was standardised for sex and age (5-year groups) using direct standardisation, and was weighted for the age-distribution of the MDC cohort. Confidence intervals were calculated assuming a Poisson distribution. Cox's regression model was used to calculate the relative risks, with adjustment for age, sex and other risk factors for stroke (BMI, diabetes, lipid lowering drug, smoking, high alcohol consumption). Oneway analysis of variance (ANOVA) with the Bonferroni post hoc test was used to compare continuous variables between the diagnostic groups. Logistic regression was used for categorical variables.

In paper III, the Students T-test, the Mann-Whitney u-test and the Pearson chi-square test were used to compare the distribution of risk factors in PICH cases and controls. A backward stepwise conditional logistic regression (p removal: 0.10) was used to adjust the relations between risk factors and PICH for potential confounders.

In paper IV, logistic regression, with sex as the dependent variable, was used to compare baseline characteristics in men and women. Logistic regression model, with fatal outcome as dependent variable, was used to explore risk factors for 28-day case fatality. The various risk factors were first entered individually. Age, gender and risk factors with $p < 0.2$ were considered to be potential confounders, and were entered in the multivariate model. Cox's proportional hazards model was used to study risk factors for 3-year mortality and stroke recurrence rates. The proportional hazards

assumption was confirmed by plotting the hazards rates for the various risk factors as a function of time.

Ethical approvals

The studies have been approved by the local ethic committee (LU 78-02 and LU 238-03).

RESULTS

Incidence of stroke subtypes in relation to country of birth

This study (paper I) was performed with participants from the Malmö 90 cohort. All Malmö citizens born in Sweden, aged 40-89 years, were compared to immigrants, aged 40-89 years, from countries with total follow-up times of $\approx >2500$ person years. In total, 113 662 persons were included in the analysis.

In total, 6082 cases of stroke were identified during the follow-up period, and 615 of these were classified as ICH. The relative risk of stroke (all types), after adjustment for age, sex, marital status and socioeconomic indicators, was higher for immigrants from Hungary and former Yugoslavia, while immigrants from Denmark, Norway, Germany, Chile, Czechoslovakia and Poland had approximately the same stroke risk as those born in Sweden (Paper I, table 2). A higher risk of PICH was observed in immigrants from China/Vietnam (Relative risk (RR), 4.2; 95% confidence interval (CI) 1.7-10.4) and former Soviet Union (RR 2.7, 95% CI 1.01-7.3).

Conclusion

The incidence of stroke and stroke and different types of stroke in Malmö, varies between immigrants from different birth countries. There are no reliable data on stroke subtype frequencies in former Soviet, but the higher incidence of ICH among immigrants from East Asia is in agreement with the previously reported higher frequencies of this type of stroke in this region. However, the extent to which genetics and environmental risk factors affect overall stroke incidence, remains to be explored.

Incidence of stroke subtypes in relation to blood pressure

In total 27 702 out of 28 449 participants from the Malmö Diet and Cancer Study were included in this study (paper II). 38.7 % were men, and mean age at screening was 58 ± 8 years. During the follow-up period 701 of the subjects suffered a stroke (613 cerebral infarction and 88 PICH).

The incidence of all stroke subtypes increased progressively with the degree of hypertension, as can be seen in figure 1. The crude and standardised incidence was highest for cerebral infarction in all blood pressure groups. The relative risk of suffering a PICH with hypertension grade 3 (BP $\geq 180/\geq 110$ mmHg) was 14.4 (95% CI, 6.4-32) as compared with BP $<140/<90$ mmHg. The corresponding relative risk of suffering a cerebral infarction was 3.4 (CI 2.6-4.5). The relative risk was highest for nonlobar PICH (figure 1). The proportion of PICH of all stroke cases, increased from 7% in the normotensive group to 19.5% in the group with hypertension grade 3.

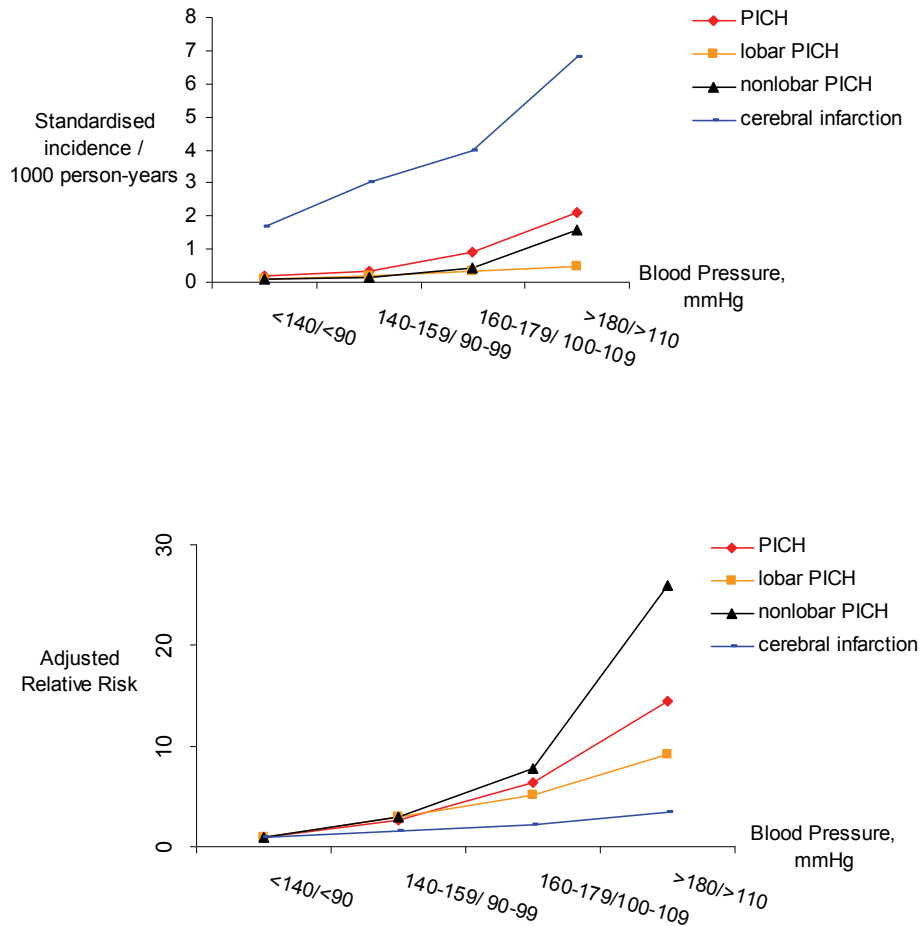


Figure 1. The standardised (age, sex) incidence respectively the adjusted relative risk of stroke subtype, in relation to blood pressure

In this study, beside elevated blood pressure, age, male sex, BMI, smoking, diabetes and alcohol consumption were independently associated with cerebral infarction. Age and male sex were also associated with PICH. Male sex and diabetes were related to nonlobar PICH, whereas age was associated with lobar PICH. The relative risk of lobar PICH for smokers was 1.97 (95% CI 0.99-3.9).

In a sub-analysis of this material (not in paper), we excluded two PICH cases with oral anticoagulation treatment at the time of stroke event. The results remained unchanged apart from for male sex which was no longer statistically significant.

Conclusion

The incidence of PICH and cerebral infarction increased progressively with increased blood pressure. Although hypertension was associated with substantially higher incidence rates and absolute numbers of cerebral infarction, which is most important in public health perspective, the relationship with PICH, especially with nonlobar location, was strongest in terms of relative risks.

Risk factors for PICH and PICH with lobar and nonlobar location

This study (paper III) was conducted with data from the Malmö Preventive Project. Risk factors in all cases of PICH during the follow-up period, in total 147 cases, were compared to 1 029 stroke-free controls (7 controls matched for age, sex and screening-year for each PICH case). 82 % were men and mean age at screening was 62 ± 7 years.

Risk factors for PICH

Compared with their respective controls, PICH patients had higher blood pressure, higher triglyceride levels and BMIs and were shorter in stature. They also had a history of diabetes, psychiatric and/or alcohol problems significantly more often, and more of them were living alone (table 2, paper III). The results from the final step in the backward conditional logistic regression analysis are given in Table 1.

	OR, last step
Systolic blood pressure (per 10 mmHg)	1.2 (1.2-1.5)
Diabetes (yes vs. no)	2.4 (1.1-5.5)
Log triglycerides	1.5 (1.04-2.1)
BMI	
Height, cm	0.97(0.95-0.998)
Alcohol abuse (yes vs. no)	
Psychiatric morbidity (yes vs. no)	1.6 (1.002-2.7)
Living alone (yes vs. no)	1.5 (0.99-2.2)

Table 1. Multivariate adjusted odds ratios (95% CI) for risk factors associated with PICH

Risk factors for lobar and nonlobar PICH

Hypertension, diabetes, high levels of triglycerides and BMI and history of psychiatric morbidity were more common in patients with non-lobar PICH than in the matched controls. Hypertension and high levels of triglycerides were more common in lobar PICH patients than in controls.

Systolic blood pressure (OR per 10 mm Hg 1.5, CI 1.3-1.7), diabetes (OR 3.5, CI 1.5-8.6) and psychiatric morbidity (OR 3.0, CI 1.6-5.6) were independently associated

with nonlobar PICH, whereas systolic blood pressure (OR per 100 mmHg 1.3, CI 1.1-1.5) and smoking (OR 2.0, CI 1.1-3.9) were associated with lobar PICH. When lobar and nonlobar cases were directly compared, no statistically significant differences were found in risk factors

Conclusion

Beside high blood pressure also diabetes, high triglyceride levels, and psychiatric morbidity were associated with PICH. In addition to high blood pressure, diabetes and psychiatric morbidity were associated with nonlobar PICH, whereas smoking was associated with lobar PICH.

Survival and Stroke Recurrence rates in patients with PICH

Prognosis and prognostic factors were established in all cases of PICH registered in STROMA between 1993 and 2000.

The mean age was 73 years, 29 % of the patients were ≥ 80 years, and 46 % were female. Beside older age in women, there were no differences in the baseline characteristics between men and women. The 28-day CFR for all PICH patients was 26 %, and the 3-year mortality rate was 49 %. In patients less than 75 years old, 20 % of the women and 23 % of the men died within 28 days ($p=0.38$). The corresponding figures for patients aged 75 years or older, were 26 % and 41% respectively ($p=0.02$).

Male sex was found to be an independent risk factor for both 28-day and 3-year mortality rates. Other independent predictors of death were age > 65 years, central and brainstem haemorrhage site, intraventricular haemorrhage, increased volume of bleeding and decreased level of consciousness.

Twelve percent of the patients had a recurrent stroke event and the stroke recurrence rate was 5.1 % per person-year. Recurrent cerebral infarction and ICH occurred at approximately the same rate. Only age > 65 years was related to recurrent stroke.

Conclusion

Women had better survival rates than men after PICH. The difference is largely explained by higher 28-day mortality in male patients older than 75 years (figure 2). However, the underlying reasons have yet to be explored

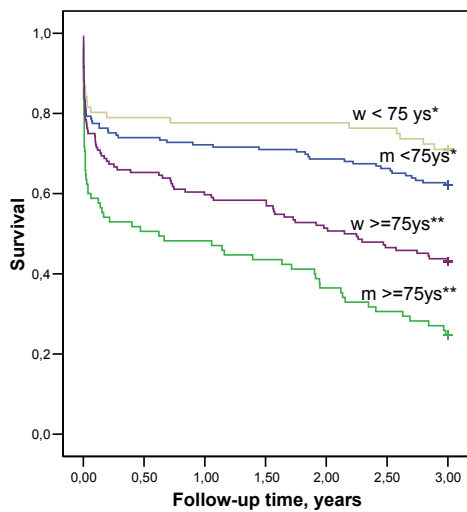


Figure 2. Survival after PICH in men (m) and women (w) above and below 75 years. * $p=0.2$, women vs men < 75 years. ** $p<0.003$, women vs men \geq 75 years.

METHOLOGICAL CONSIDERATIONS

A proposal of criteria for an ‘ideal epidemiologic stroke study’ was first made in 1987¹⁹² and has then been revised, lately in 2004⁵⁸ (table 2).

Domains	Core Criteria	Supplimentary Criteria
Standard definitions	<p>World Health Organisation definition of stroke</p> <p>At least 80% CT/MRI verification of the diagnosis of ischemic stroke, intracerebral hemorrhage, and subarachnoidal hemorrhage</p> <p>First-ever-in-lifetime stroke</p>	<p>Classification of ischemic stroke into subtypes (eg, large artery disease, cardioembolic, small artery disease, other)</p> <p>Recurrent stroke</p>
Standard methods	<p>Complete, population-based case ascertainment, based on multiple overlapping sources of information (hospitals, outpatient clinics, general practitioners, death certificates)</p> <p>Prospective study design</p> <p>Large, well-defined, and stable population, allowing at least 100 000 person-years of observation</p> <p>Follow-up of patients’ vital status for at least 1 month</p> <p>Reliable method for estimating denominator (census data \leq 5 years old)</p>	<p>Ascertainment of patients with TIA, recurrent strokes and those referred for brain, carotid, or cerebrola vascular imaging</p> <p>“Hot pursuit” of cases</p> <p>Direct assessment of under-ascertainment by regular checking of general practitioners’ databases and hospital admissions for acute vascular problems and cerebrovascular imaging studies and/or interventions</p>
Standard data presentation	<p>Complete calendar years of data; \leq5 years data averaged together</p> <p>Men and women presented separately</p> <p>Mid-decade age bands (eg 55 to 64 years) used in publications, including oldest age group (\geq 85 years)</p> <p>95% confidence interval around dates</p>	<p>Unpublished 5-years age bands available for comparison with other studies</p>

Table 2. Gold standard for a stroke incidence study, according to Feigin et Carter, 2004.

Study design

In paper I-III, the information of risk factors was collected before the stroke event or death. Due to the prospective design, assessment of risk factors was not influenced by stroke event. However, we do not know whether some risk factors have changed on the individual level during the long follow-up period, in particular in the MPP cohort (paper III), but also in the MDC (paper II). As participants with detected vascular risk factor at baseline examination were referred for further evaluation and treatment, it is plausible that these individuals have a reduced risk for stroke during the follow-up time. However, we lack information on the proportion of participants in the cohorts that received treatment after referral. If anything, it should be expected that the relationship in our studies would be even stronger in a population which have not received interventions.

In addition, a change of exposure over time would have diluted the observed associations. Instead, in paper II, the differences between the blood pressure groups increased continuously over the entire follow-up period (Fig 3).

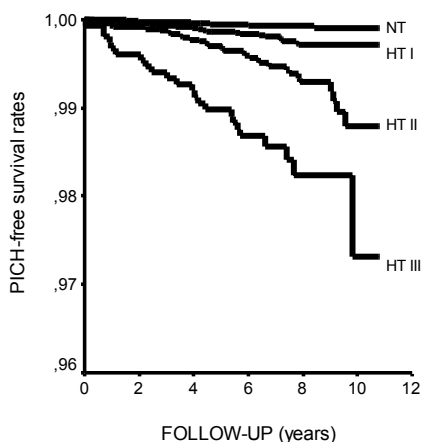


Figure 3. Crude incidence of PICH in relation blood pressure category (NT <140/90 mmHg; HT I, 140-159/90-99 mmHg; HT II, 160-179/100-109 mmHg and HT III, $\geq 180/\geq 110$ mmHg)

In Göteborg, Sweden, the frequency of hypertension, smoking and hypercholesterolemia was found to decrease in men and women between 1987 and 2006, whereas diabetes and BMI increased in men.¹⁹³ We can thus not exclude the possibility that participants included in the cohort studies later were healthier with regard to vascular diseases than those who were recruited early in the study. To avoid that variations in the characteristics of populations over time influence the results, a nested case-control design was used in the third study (Paper III, MPP cohort). The PICH cases were matched with controls of the same age, sex and screening year. However, this prevented the effects of age and sex on the incidence of PICH from being studied. In the MDC the screening period was five years, and a prospective cohort design was used in paper II. Paper IV describes a prospective observational

study. Information on haemorrhagic characteristics, clinical data and vascular risk factors were assessed without knowledge of the patients' outcome.

Representativity of the study population

The attendance rate in the MPP study was 71%, but only 41% in the MDC. Similar decline in attendance rates during the last decades is observed by others.^{194, 195} Generally, non-participants (i.e. invited to participate, but for various reasons did not) in health screening programs have less favourable health and/or socioeconomic situation.^{194, 196-198} This is reflected in the MPP¹⁹⁹ and in the MDC¹⁷⁹ cohorts by a higher total mortality in non-participants as compared to participants. With respect to the general population, there might be an under-estimation of the associations we found in paper II and III. However, non-invited birth cohorts of men who were compared to those invited in the MPP, did not differ with respect to overall and cardiovascular mortality.¹⁹⁹

Quality of stroke ascertainment

Cases with stroke diagnosis were achieved from three different sources; STROMA (paper I-IV), The Swedish hospital discharge register and The Swedish cause of death register (paper II-III).

In STROMA, the CT frequency increased from 64.3 % to 98.3 % between 1989 and 2001, with the largest increase between 1991 and 1992. This threshold is the reason for the chosen time period in paper IV (1993-2000). The reduced proportion of unspecified stroke corresponded closely to an increased proportion of cerebral infarctions. This suggests that most unspecified stroke were due to cerebral infarction. Overall, few cases of ICH seems to be hidden in the category unspecified stroke, irrespectively of the source of case ascertainment, as indicated in table 3.

Source	ICH (ICD 431/I61.0-9)	UND (ICD 436/I64.0-9)	PICH
STROMA	78 (73*)	12 (0)	73
Cause of Death Register**	11 (11)	7 (1)	12
National Patient Register**	8 (3)	54 (0)	3
Total	97	73	88

Table 3. Number of identified ICH and stroke UND in different sources of case ascertainment procedure in paper II. () indicate the number of verified PICH. * = 5 cases were secondary ICH. ** = cases outside Malmö.

The screening process applied to the STROMA database includes a daily broad search among patients admitted to the hospital. The hospitalisation rate of stroke patients in Malmö between 1993 and 1998 was 95 %.²⁰⁰ The additional 5 % either died at the emergency ward (0.3 %) or were treated as outpatients (4.7 %). The case ascertainment, however, does not include screening in the primary care databases. In other stroke registers 1.6 %²⁰¹ respectively 3.7 %²⁰² of identified stroke patients were

found by such supplementary searching. These patients were not examined at the hospital, and in Lund, Sweden,²⁰² 86 % were living in nursing homes. Up until 1995 a systematic active search for stroke cases in nursing homes was included in the case-identification process in STROMA. It was found that all cases of suspected stroke had been referred for CT examination and hence included through the case-identification process at the hospital. Anyhow, some non-hospitalised patients might have been missed, and we can not exclude that there were changes in referral praxis between 1996 and 2001. Stroke severity is higher in ICH as compared to cerebral infarction,²⁰³ and it is likely that a majority of the non-hospitalised stroke cases suffered a cerebral infarction.

It can not be ruled out that some patients died as a result of stroke before reaching the hospital. Others reported a pre-hospital PICH mortality of 6%¹³⁰ respectively 7%.¹²⁹ However, a review of all autopsy records of out-of-hospital deaths in Malmö, in 1989 and 1990, revealed only 7 missed cases in STROMA (0.6% of all stroke events) during these two years.²⁰⁰ Cases with identified cerebral infarction in paper I and II were for practical reasons (large number and clinical diagnosis) not scrutinised in the case ascertainment procedure as cases with suspected ICH and undefined stroke. We can not rule out that some cases with ICH were miscoded as cerebral infarction.

Haemorrhage characteristics

We used the ABC/2-formula in estimation of the bleeding volume. The formula ABC/3 was recently recommended, in cases of irregularly and separately shaped bleedings, which is often the case in OAT-induced bleedings.²⁰⁴ However, calculating the volume as ABC/2 formula tends to overestimate the volume,²⁰⁴ so this probably does not explain why the volumes calculated in this work were in the lower range compared with other studies, in particular in OAT-induced bleedings.^{153, 205} It has been estimated that in approximately a quarter of the cases, the haemorrhage volume expands during the first hours.^{148, 206} The smaller bleeding volumes reported in our study may partly be due to early hospital-admission and thus early CT examinations in our centre. However, we lack information on time from stroke onset to the time of CT-scanning, as well as a second CT examination (to evaluate haemorrhage growth), and no further conclusions can be made.

Risk factors

The associations between the vascular risk factors (as blood pressure, smoking, lipids) and incidence of stroke and cardiovascular disease have been verified in many previous studies from MPP and MDC.²⁰⁷⁻²¹⁰

In the MDC (paper II), we lacked values of blood glucose and lipids. However, the percentage of diabetes in PICH and the association with nonlobar PICH, is in line with the results from the MPP cohort (paper III), where diabetes diagnosis was assessed by blood glucose level as well as self reported diabetes.

The percentage of smokers was lower in the MDC as compared to the MPP. There are several possible explanations for this difference. First, there was a decline of smoking

in the general population during this time period.¹⁹³ Then, smoking¹⁹⁵ could be more common among non-responders, and the rate of non-responders was higher in MDC compared with MPP. Nevertheless, smoking was an independent risk factor for lobar PICH in the MDC, and in the MPP smokers had a relative risk for lobar PICH of 1.97 (95 % CI: 0.99-3.9). A limitation with prospective cohort studies is that the risk factor arsenal is restricted to what was of most interest and reasonable achievable at the time of the initial study design. As a consequence in our studies, we lack information of for example cholesterol fractions, hemostatic parameters, antitrombotic medication and genetic factors.

Missing value

In Malmö 1990 cohort (paper I), 0.04 % participants lacked information of birth country and in the MDC (paper II), 1.5 % out of 28 449 participants had missing information of one or more risk factors. These participants were not included in the studies, and we can not rule out that exclusion of these participants might have influenced the results. In the MPP (paper III), only a computer based questionnaire was used. The participants could choose between a 'yes' or 'no' answer. For technical limitations at the time, a 'non-answer' was coded as 'no', so we cannot differentiate between these two answers, or estimate the actual rates of missing values, which is a limitation. In the prognosis study (paper IV), information on vascular risk factors was obtained from medical records and the frequency of missing data on vascular risk factors was considerable (hypertension n=79 (16.7 %), smoking n=191 (40.3 %), ischemic heart disease n=77 (16.2 %) and diabetes n=83 (17.5 %). Information on the level of consciousness at admission and intraventricular haemorrhage was missing in 5 and 9 cases respectively. In order not to loose power in the multivariate analysis, missing values were coded as a separate category.

GENERAL DISCUSSION

The main purposes of this thesis were to evaluate risk factors and prognosis of PICH. In epidemiological studies, a risk factor indicates that the persons which are exposed to the risk factor have higher risk to develop the disease as compare to the unexposed, an information that might have implications in preventive work for example.

It has been claimed that 'attempts to infer the underlying disease by analysis of clinical risk factors...is at best an approximation of what would be learned by microscopy',²¹¹ however, it must be borne in mind that the incidence of PICH is low, and the post-mortem examinations may not always be carried out for various reasons, including ethical concerns. Therefore, the amount of information available from such studies is limited. The results of epidemiological studies do not prove what causes a particular disease in terms of cellular pathology, but the information obtained may help us to understand the development of the disease, i.e. the aetiology.

Accurate prognoses are important for several reasons. Apart from providing the patient and relatives with information on the expected outcome, prognoses can be used in the design of research projects and the assessment of care facilities. Only twelve community-based studies on prognosis following PICH had been carried out up until 2000, and the number of participants included did not exceed 122.²¹² The increasing interest in this rare stroke subtype during the past decade is mirrored by the increasing number of community-based publications on prognosis.^{18, 53, 128-130} In order to obtain reliable information on the risk factors and prognosis concerning less common diseases, large cohorts are required. In addition, reliable case ascertainment and diagnosis are crucial. Few individual study centres can fulfil these requirements, and the majority of previous studies on prognosis are multicentre studies.^{53, 128-130}

In prospective large-cohort studies, stroke diagnosis is often obtained from hospital and/or national discharge registers.^{72, 74, 80, 83} In this work, information was obtained from a local stroke register, employing a broad case-retrieval procedure, in addition to national registers, which improve the case finding possibilities.²¹³ The next step is to verify the stroke diagnosis. For practical reasons it is seldom possible to verify each potential stroke case in large epidemiological studies, especially as the diagnosis of cerebral infarction is mainly based on clinical information. PICH diagnosis, on the other hand, is based on characteristics seen in CT and/or MRI examinations. In this work the same emphasis was placed on diagnosis verification regardless of the source of information on cases.

Relation between country of birth and intracerebral haemorrhage

Previous studies have shown differences in the incidence of stroke between individuals of different ethnic origin living in the same country,^{59-61, 66} although such studies are not common. The assignment of ethnicity may vary, and self-reported ethnicity has been suggested to be the optimal method.²¹⁴ By using ethnicity as a marker, the

heterogeneity of the cohort will be increased by second- and third-generation immigrants who have adopted the lifestyle of their new country and are exposed to its environment. On the other hand, self-reporting of country of birth, as used in the present work, may lead to erroneous classification of ethnicity. For example, second-generation immigrants would give their country of birth as Sweden, although they belong to a different ethnic group. In spite of the small numbers in the groups of people born in another country, we observed a higher risk of ICH in immigrants from China/Vietnam and the former Soviet Union than in participants born in Sweden. This is in accordance with the high rates of ICH reported in Asia,^{54, 64, 74, 215, 216} and the higher rate of ICH among Chinese immigrants compared with Whites in New York (USA).²¹⁷

According to the results of the MONICA project (Monitoring of Trends and Determinants in Cardiovascular Disease, by the World Health Organization), the overall stroke rate in Moscow and Novosibirsk, Russia, was high.²¹⁸ According to another study published by the WHO, the highest stroke mortality rates were observed in Eastern Europe and the countries of the former Soviet Union.²¹⁹ There are no reliable incidence data on different stroke subtypes in the Soviet Union⁷, but a high rate of ICH has been reported in Georgia.²²⁰

The elevated stroke burden in East Asia and the former Soviet Union could be explained by high rates of hypertension²²¹ and diabetes.²²² High alcohol consumption in the former Soviet Union²²³ probably also influences the risk of stroke. Even 20 years after migration from China to the USA, hypertension was still the most important risk factor for stroke among Chinese stroke patients²²⁴ and more prevalent as compared with stroke patients with other ethnicities.²¹⁷ The overall stroke mortality rate was found not to differ between Chinese immigrants and Whites, and was significantly lower than the mortality rate among Chinese in China during the same period,²²⁵ indicating that genetic factors had less influence than environmental factors.

Previous studies on the population in Malmö have shown higher incidences of stroke in areas with low socioeconomic conditions and a large proportion of immigrants.¹²⁴ Low income and living alone influence health care costs in Malmö, in contrast to country of birth.²²⁶ However, the extent to which the continued high risk of ICH among immigrants from East Asia and the former Soviet Union seen in the present work can be attributed to genetic factors, rather than lifestyle, vascular risk factors or lower use of health care services has yet to be explored.

Blood pressure and stroke

In prospective studies, risks are often expressed in terms of relative risks for the sake of convenience. However, in order to assess the clinical and public health implications, relative risks must be translated into the number of incidences during a specified period of time. Few studies have compared the incidence of stroke subtypes, in terms of absolute and relative risks, in relation to hypertension. In this work it was found that elevated blood pressure is associated with a higher risk of PICH in terms of relative risk. However, in terms of the number of cases, i.e. the standardised incidence during a

defined period of time, elevated blood pressure is associated with a greater number of cases of cerebral infarction. The standardised incidence of cerebral infarction, classified according to age and sex, increased with higher blood pressure (hypertension grade 3), from 1.7 to 6.8 per 1000, while the corresponding incidences of PICH increased from 0.2 to 2.1 per 1000. These figures reflect the numbers of patients expected to suffer a stroke, and thus the importance of hypertension on stroke incidence from a public health perspective.

As reported in a previous publication by our group, uncontrolled hypertension, despite pharmacological treatment, is highly prevalent.²⁰⁸ We lack information on treatment compliance, but an Australian case-control study showed a nearly five-fold elevated risk of PICH when medication for hypertension was not taken.²²⁷ Others have estimated that the treatment of patients with hypertension could prevent 17 to 28% of haemorrhagic strokes (including subarachnoidal haemorrhages).²²⁸ They did not report blood pressure levels, but in our cohort the mean blood pressure levels were higher than recommended¹⁸⁶ in all treated groups. This further indicates the importance of blood pressure control in preventing PICH.

Relative risks depend entirely on the risk of the reference group. PICH, as compared to cerebral infarction, is unusual in normotensive individuals, which could explain why the gradient of the RR associated with blood pressure is steeper for PICH than for cerebral infarction. However, it also underlines the strong relationship between elevated blood pressure and PICH, while other risk factors (e.g. smoking, diabetes, alcohol and BMI) are also important for the incidence of cerebral infarction.

Risk factors for lobar and nonlobar PICH

The first prospective large-cohort studies on risk factors for stroke did not differentiate between ischaemic and haemorrhagic stroke.^{80, 229} Knowledge of the differences in stroke aetiology and the introduction of CT imaging in the diagnostic procedure have later contributed to separate analysis of these two subtypes.^{72, 78, 83, 108} In the present work it was found that subdivision according to the site of haemorrhage in PICH enhanced the possibility of identifying predictive factors for PICH. For instance, diabetes was independently related to non-lobar PICH and smoking to lobar PICH.

A higher prevalence of diabetes in patients with non-lobar PICH as compared to those with lobar PICH was reported in a case-control study,¹⁰⁷ and is in line with the present results. Diabetes is strongly associated with increased severity of extracranial atherosclerosis assessed by means of carotid intima-media thickness,²³⁰ autopsy-verified coronary artery disease²³¹ and angiography-verified peripheral artery disease.²³² Although diabetes is correlated to both small- and large-vessel-related cerebral infarctions,²³³ the association with specific intracranial vasculopathy is less clear²³⁴. In fatal stroke, diabetes is independently related to the prevalence of intracranial atherosclerotic plaque.²³⁵

Smoking is also related to a range of atherosclerotic manifestations,^{232, 236} but biological evidence of an association with specific cerebral vascular pathologies is less

clear.^{10, 234} Autopsy of the circle of Willis and its major branches, performed on samples in a prospective study (the Honolulu Heart Study), showed an association with smoking and atherosclerosis in the larger, but not the smaller branches.²³⁷ A positive relation has been observed between smoking and ICH with increasing age in men.²³⁸

Smoking is linked to the formation of aneurysms.²³⁹ We can not exclude that some cases with vascular malformations were missed in the lobar PICH groups.^{240, 241} The diagnostic procedure to identify vascular malformations as the cause of the haemorrhage involves catheter angiography, an investigation with relatively high risks, and is only performed in certain cases.¹⁶³ No data are available on the use of angiography in patients with intracerebral haemorrhage at our hospital. The decision to perform angiography is often made in collaboration with colleagues from the neurosurgery and neuroradiology departments. Although speculative, smoking-induced microaneurysms might explain the relation to lobar PICH.²⁴²

The results obtained in this work suggest that elevated blood pressure is related to both non-lobar and lobar PICH, but in particular to non-lobar. It has been postulated that an acute increase in blood pressure or cerebral blood flow may cause rupture of perforating arteries by inducing fibrinoid necrosis (the acute form of arteriolosclerosis) in vessels with or without former vasculopathy.^{40, 243} Physiologically, the arterioles serve as resistance vessels, responsible for the autoregulation of the cerebral blood flow. The capacity of these vessels to dilate and contract as the result of various stimuli is crucial for their autoregulatory function.^{244, 245} It has been suggested that impaired autoregulation due to arteriolosclerosis makes the most distal and smaller arterioles more sensitive to the influence of elevated blood pressure, with secondary smooth muscle damage and possible rupture as a consequence.⁴⁴ However, CAA, also leads to impaired vessel elasticity and the variation in pulse pressure was proposed to explain the distribution of CAA and arteriolosclerosis. The pulse pressure within the cerebral vessel tree is higher in the deep parts of the brain, i.e. close to the feeding vessels of the brain, which makes the non-lobar arterioles more susceptible to increased blood pressure, as compared with the lobar located arterioles. On the other hand, the high pulse-pressure may protect the non-lobar vessels from amyloid deposition.²⁴⁶

Symptoms of depression are related to increased risk of cerebral infarction.¹¹⁶⁻¹¹⁹ It is interesting to note that, although we used a rather unspecific definition of psychiatric morbidity, participants who ‘had received treatment or care for nervous or psychiatric problems at some time’ had a clearly increased risk of suffering PICH, in particular non-lobar PICH, an average of fourteen years later. One explanation of this could be a less healthy lifestyle and poor compliance with treatment (for example not taking antihypertensive medication) among those with psychiatric disorders.^{120, 247} The strong association to non-lobar PICH remains to be evaluated. The questionnaire did not differentiate between psychiatric diagnoses and lacked information on the time of mental illness. Patients with depression have decreased cerebrovascular reactivity, independently of classical vascular risk factors.¹²² Decreased cerebrovascular reactivity is a sign of impaired elasticity of the arteriolar vessels, and is observed in

arteriosclerosis-related diseases such as lacunar infarction.²⁴⁸ Interestingly, APOE ε2, which is associated with lobar PICH, is not related to depressive disorders.²⁴⁹

Prognosis

It was established that of the patients admitted to Malmö University Hospital between 1993 and 2000 with first-ever PICH, approximately a quarter died within one month, and half within three years. These low fatality rates, compared with other studies, could reflect low PICH severity (small bleeding volume) as well as more efficient patterns of care, but may also be explained by a combination of differences in study sample and study design. For example, we included only patients with first-ever PICH, which means lower comorbidity in terms of previous brain lesions. Other differences include admission rates of various centres and ethnicity, which could influence PICH and stroke mortality.^{135, 250}

The better survival in women could largely be explained by better survival in female patients aged over 75 years. This is in accordance with previous studies on stroke patients,^{138, 251} but to our knowledge this has not been demonstrated specifically for PICH. In the general population, men are at higher risk of cardiovascular disease,²⁵² and a similar relationship has been reported in stroke patients^{138, 139}. This is reflected by the lower age of men at the time of their first PICH event. In the present work, no significant differences were found between men and women in cardiovascular comorbidity, except for smoking, which was more frequent among men, but a high percentage of data was missing. Differences in mortality could also be explained by differences in management. In Sweden, women with ischaemic stroke due to atrial fibrillation received anticoagulant treatment less often than men.¹⁴¹ However, a recent study in Denmark showed no sex-related differences in acute hospital care among stroke patients, including early admission to the stroke unit, early CT, and treatment with antiplatelet or anticoagulant therapy.²⁵³

In clinical practice, early prognosis is often desired by both care-givers and relatives of the patient. Although scores can be calculated based on information from the acute phase, including haemorrhagic characteristics and level of consciousness,^{145, 146} prognosis is a complicated task. In fact, in a single-centre study, it was found that the physicians tended to be pessimistic in early prognosis after ICH, with self-fulfilling prophesy of poor outcome as a consequence.²⁵⁴ The level of consciousness often has considerable influence on the decision to give early “do not resuscitate” orders.²⁵⁵ However, few studies have presented survival rates in unselected PICH patients who were unconscious on admission to the hospital.^{54, 130} In the current work, 25% of the unconscious patients survived four weeks and 6 patients out of 19 could return to their own homes or to rehabilitation ward, although with major neurological deficits. Future studies on outcome should perhaps consider predictive factors in the sub-acute state as baseline as well.

FURTHER RESEARCH

In the present thesis the value of separate analysis of PICH subtypes was highlighted. As a consequence of the development of new diagnostic tools, the possibilities of detecting secondary causes of ICH, and hence the potential to study well-defined subtypes of primary intracerebral haemorrhage, have been improved since the performance of the present studies.

Large haemorrhage volume is the single most important predictor of bad outcome. Ongoing expansion may be detected by radiological evaluation. Little is known, however, about which factors are associated with haemorrhage volume and volume expansion. Basically, the factors that were found to be associated with increased risk of PICH in our studies might as well be associated with haemorrhage volume by their effects on endothelial level.

Atherosclerosis is an inflammatory process in the vessel wall. A number of inflammatory markers have been found to be associated with increased risk of cerebral infarction. Although small vessel disease, an atherosclerosis related process, seems to underly nonlobar PICH, previous studies did not find a relation between inflammatory markers and PICH. Studies on this topic, with specific analysis on PICH subtypes might be of value.

In addition, manifestations that might be related to PICH, as for example cerebral microbleeds, are detected by newer MRI methods. Histopathological analysis and population-based data on apolipoprotein E genotype support that the distribution of microbleeds might be related to specific underlying vasculopathologies. The predictive value of cerebral microbleeds in people with and without former stroke, as well as the correlations to classical and new vascular risk factors are subjects for further evaluation. These results could have implications for our understanding of the underlying mechanisms and thus for stroke prevention.

CONCLUSIONS

In the city of Malmö, southern Sweden, the incidence of stroke and stroke subtypes varies between immigrants from different countries. An increased incidence of ICH among immigrants from China/Vietnam and the former Soviet Union, as compared to the incidence among citizens born in Sweden, was observed. This reflects the higher rate of stroke in these countries as well as the higher rate of ICH in Asia. The extent to which this results are caused by genetic, vascular, environmental and/or socioeconomic factors remains to be evaluated.

The incidence of primary ICH (PICH) and cerebral infarction increased with increasing blood pressure. Although hypertension was associated with substantially higher incidence rates and absolute numbers of cerebral infarction, which is most important in the public health perspective, the relationship of PICH to hypertension, especially with non-lobar location, was strongest in terms of relative risk.

Increasing age and male sex were associated with PICH. Besides high blood pressure, diabetes, high triglyceride levels and psychiatric morbidity were modifiable risk factors for PICH.

Diabetes and psychiatric morbidity were independent risk factors for non-lobar PICH, whereas smoking and high age were associated with lobar PICH.

Approximately a quarter of the patients admitted for first-ever PICH died within one month, and half died within three years. Besides haemorrhage volume, intraventricular haemorrhage, higher age and brainstem or central haemorrhage site were also associated with early fatality.

Women exhibited better survival than men after PICH. The difference is largely explained by higher 28-day mortality in male patients aged over 75 years. However, the underlying reasons are yet to be explored

Twelve percent of the patients had a recurrent stroke event and the stroke recurrence rate was 5.1 % per person-year. Recurrent cerebral infarction and ICH occurred at approximately the same rate. Only age > 65 years was related to recurrent stroke.

ACKNOWLEDGMENTS - Tack

Alla **patienter** med hjärnblödning jag träffat på neurologen – era frågor har i hög grad bidragit till frågeställningarna i denna avhandling. **Studiedeltagare** i Malmö Kost Cancer och Malmö Förebyggande Medicin för att ni tog er tid att delta i de omfattande undersökningarna

Gunnar Engström, huvudhandledare. Jag är oändligt tacksam för att du öppnat portarna till de 'stora kohorterna' och över hur du lotsat mig genom epidemiologins ibland lite snåriga djungel, liksom genom projektet i stort. Alltid med tålmod, briljans, effektivitet, vänlighet och uppmuntran. Och visst har du rätt, allt kan inte upptäckas med mikroskop

Hélène Pessah-Rasmussen, biträdande handledare, för att du under drygt tio år delat med dig av din samlade erfarenhet, inte bara inom ramen för detta projekt, med största generositet, omtänksamhet, kunskap, entusiasm och vänskap. Oavsett längden på våra möten, gav du alltid kreativa råd som ledde projektet framåt. Muchas gracias

Bo Norrving, biträdande handledare, för uppmuntran, vänlighet, konstruktiva synpunkter och inte minst tillgänglighet - trots dina uppdrag världen över. Din breda kunskap om stroke har varit ovärderlig och det har varit en ära att få arbeta med dig. Tusen tack

Bo Hedblad, forskargrupschef, för möjligheten att arbeta i din grupp och för fint arbetsklimat. Dina intressanta tankar kring studieupplägg, resultat och manus har varit inspirerande och viktiga inslag under arbetets gång

Farhad Ali Khan, forskarkollega, för att du frikostigt delade med dig av din erfarenhet, hjälpte mig med databas, gav konstruktiv kritik och för trevligt samarbete.

Ingela Jerntorp, forskningssjuksköterska och STROMAs noggranna väktare. Ditt vänliga bemötande, oavsett längden på mina listor, har ofta räddat dagen

Bortgångne Professor **Lars Janzon**, min tidigare forskargrupschef. Med sällsynt förmåga att lyfta fram nya aspekter både avseende frågeställning och fynd var han en sann inspiratör för mig

Cairu Li, Sofia Gerward och **Lena André-Petersson** – trivsamt småprat i korridoren kan leda långt

Bortgångne **Toivo Matilainen** som vänligt och tålmodigt undervisade mig i bedömning av CT-bilder. Övriga kolleger på neuroröntgen, UMAS, **Pavel Maly**, **Anita Strömbeck**, **Kasim Abul-Kasim** och **Angelica Overgaard** för att även ni tog er tid att hjälpa till då jag stötte på patrull

Göran Berglund för att jag fick ta del av MPP-materialet och för medförfattarskap

Peter Svensson, för värdefulla uppgifter angående waran-behandling och för medförfattarskap

Alla medarbetare på neurologiska kliniken. Speciellt tack riktas till

Marco Brizzi, min mentor, för din uppmuntran och fantastiska flexibilitet som i hög grad bidragit till att projektet kunde ros i hamn. Din aldrig sinande entusiasm avseende neurologi och främst akut strokevård är och har varit både stimulerande och smittsam
Jesper Petersson, för många givande diskussioner kring fall och projekt samt för din generositet med tid för forskning

Kjeld Hougaard, för uppmuntran från start och för undervisning utöver det vanliga
Luisa Bassini och **Elisabeth Ristic** för hjälp med journaler.

Margareta Ståhl för hjälp med bokning så att ekvationen klinik/forskning gick ihop
Stroke-teamet och arbetsgruppen bakom Unga Stroke, för gott samarbete. Det har haft stor betydelse för att hålla glöden vid liv

Pernilla Sandgren, **Maria Macek**, och **Erik Campbell**, för samarbete i ICH-projektet inom Unga stroke, även om studien inte kom med här. **Pia Apt**, för det fina kontrollmaterialet

Nina Brag-Petersson, **Ursula Heldmann** och **Åsa Nilsson**, mina toleranta rumskamrater, för pratstunder där vi fann lösningen på de mest närliggande världsproblemen

Magnus Wahlquist, **Mats Rosvall** och **Fredrik Buchwald** för trevligt samarbete överlag. Mats och Magnus - för att ni, utan hörbara suckar, tog er an de många schemaändringar jag orsakade

Frans-Thomas Fork, för tips from the coach, inte minst under studietiden

Martin Stjernquist, handledare under FÖS, för inspiration att arbeta med kärrelaterade problem

Eva Andersson, Arkivcentrum, för effektivitet och hjälpsamhet

och hemmavid

Tina M, **Sanna M**, **Emily W**, **Karin J**. Geografiskt nära eller långt borta - uppmuntrande väninnor i stort och smått

Claudia och **Christian**, mina syskon med familjer, **Leonardo**, **Petra** & gossarna, **Immi**, **Severino** & **Marianne** för ovärderligt stöd, vänskap och glädje.

Britt och **Armando**, mina fantastiska föräldrar, för allt – det jag lagt märke till och främst det som gått mig obemärkt förbi. Grazie di cuore!

Paolo – min Kärlek. **Anna**, **Dante**, **Isac**, **Oscar**, **Leonardo** och **Isabella** – alla frånvarande svar, missade Bollibompa, fotbolls- basket och gympapass, lek- gos och pratstunder - det var det såklart inte värt. Ni är underbara och har varit fantastiskt tålmodiga, speciellt under slutspurten <3

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LUND UNIVERSITY
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Lund University, Faculty of Medicine Doctoral Dissertation Series 2009:68

ISBN 978-91-86253-56-1

ISSN 1652-8220