Risk Stratification in Ischemic Stroke

Clinical and Radiological Risk Scores for Stroke Recurrence Prediction in Non-atrial Fibrillation Ischemic Stroke Patients

Andersen, Søren Due

DOI (link to publication from Publisher):
10.5278/VBN.PHD.MED.00059

Publication date:
2016

Document Version
Publisher's PDF, also known as Version of record

RISK STRATIFICATION IN ISCHEMIC STROKE

CLINICAL AND RADIOLOGICAL RISK SCORES FOR STROKE RECURRENCE PREDICTION IN NON-ATRIAL FIBRILLATION ISCHEMIC STROKE PATIENTS

BY
SØREN DUE ANDERSEN

DISSERTATION SUBMITTED 2016

AALBORG UNIVERSITY
DENMARK

RISK STRATIFICATION IN ISCHEMIC STROKE

CLINICAL AND RADIOLOGICAL RISK SCORES FOR STROKE RECURRENCE PREDICTION IN NON-ATRIAL FIBRILLATION ISCHEMIC STROKE PATIENTS

by

Søren Due Andersen

AALBORG UNIVERSITY
DENMARK

Dissertation submitted 2016

.

Dissertation submitted: May 6, 2016

PhD supervisor: Torben Bjerregaard Larsen
Associate Professor, MD, PhD, FESC
Department of Clinical Medicine
Aalborg University

Assistant PhD supervisors: Flemming W. Bach
Professor, DMSc
Aarhus University &
Department of Neurology, Aarhus University Hospital

Anders Gorst-Rasmussen
MSc, PhD
Unit of Clinical Biostatistics
Aalborg University Hospital

PhD committee: Clinical Professor Jeppe Hagstrup Christensen (chair.)
Aalborg University

Clinical Associate Professor, Søren Paaske Johnsen
Aarhus University

Professor in Neurology, Halvor Næss
Haukeland University Hospital

PhD Series: Faculty of Medicine, Aalborg University

ISSN (online): 2246-1302
ISBN (online): 978-87-7112-700-3

Published by:
Aalborg University Press
Skjernvej 4A, 2nd floor
DK – 9220 Aalborg Ø
Phone: +45 99407140
aauf@forlag.aau.dk
forlag.aau.dk

Printed in Denmark by Rosendahls, 2016

PREFACE

This PhD dissertation is the result of collaboration between the Department of Neurology, Aalborg University Hospital and Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Faculty of Health, Aalborg University, Denmark. The work was carried out during my employment at these departments in the period 2013-2016.

I owe a debt of gratitude to a number of people who made this project possible. First, I wish to thank my supervisors, Torben Bjerregaard Larsen, Flemming Bach and Anders Gorst-Rasmussen, who all, in their unique manner, have rendered invaluable supervision during the process and in the completion of the project.

I want to thank Yousef Yavarian, Department of Radiology, for the training and support doing the image analyses, and Flemming Skjøth for statistical and epidemiological support, especially in the last phase of the work. Also, I owe my thanks to Jette Nordstrøm Kjældgaard for her pertinacious work with creating the datasets. A great thankyou goes to Gregory Lip for the ideas upon which a great part of this dissertation is based and for the invaluable comments and suggestions to all the papers of the dissertation. Not least, I want to thank Michael Nielsen, Department of Neurology, who played a pivotal role in initiating the project. And finally, I want to thank the PhD students at Aalborg Thrombosis Research Unit for the informal, but highly appreciated help during my work.

The project was supported by a grant from the Heinrich Kopp Foundation.

Søren Due Andersen

The dissertation is based on the following studies:

1. Andersen SD, Gorst-Rasmussen A, Lip GYH, Bach FW, Larsen TB. Recurrent Stroke – The Value of the CHA_2DS_2VASc Score and the Essen Stroke Risk Score in a Nationwide Stroke Cohort. *Stroke*. 2015;46:2491-2497

2. Andersen SD, Larsen TB, Gorst-Rasmussen A, Yavarian Y, Lip GYH, Bach FW. White Matter Hyperintensities and Clinical Risk Scores in Recurrent Ischemic Stroke. *Cerebrovascular Diseases.* 2016. Submitted

3. Andersen SD, Skjøth F, Yavarian Y, Bach FW, Lip GYH, Larsen TB. Multiple Silent Lacunes are Associated with Recurrent Ischemic Stroke. *Cerebrovascular Diseases.* 2016;42:73-80

LIST OF ABBREVIATIONS

AF: Atrial fibrillation

$CHADS_2$: Acronym for congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, previous stroke or TIA (2 points).

CHA_2DS_2VASc: Acronym for congestive heart failure, hypertension, age ≥ 75 years (2 points), diabetes mellitus, previous stroke or transient ischemic attack (2 points), vascular disease, age 65-74 years, and sex class (female).

CI: Confidence interval

CT: Computed tomography

DWMH: Deep white matter hyperintensities

ECG: Electrocardiogram

HR: Hazard ratio

IQR: Interquartile range

LiLAC: Life Long After Cerebral ischemia

MRI: Magnetic resonance imaging

NRI: Net reclassification improvement

OR: Odds ratio

PVH: Periventricular white matter hyperintensities

SD: Standard deviation

TIA: Transient ischemic attack

TOAST: Trial of Org 10172 in Acute Stroke Treatment

WHO: World Health Organization

ENGLISH SUMMARY

In Denmark, nearly 11,000 people suffer from stroke every year. Worldwide, stroke is the second leading cause of death and the most frequent cause of acquired disability.

About 85% of all strokes are of ischemic origin. The 5-year cumulative risk of ischemic stroke recurrence after an incident ischemic stroke reaches 32% in some studies. Therefore, initiatives to prevent stroke recurrence are an essential part of the medical therapy following ischemic stroke. The risk of ischemic stroke recurrence is not uniformly distributed among patients. Some patients have a risk considerably above the average risk of recurrence, and some patients have a risk considerably below the average risk of recurrence. At present, all patients except those with atrial fibrillation receive the same kind of medical therapy after ischemic stroke. However, in a future perspective, valid risk stratification tools may help clinicians provide a more individualized treatment that strikes an optimal balance between risks and benefits.

The CHA_2DS_2VASc score is a risk score scheme developed for stroke and thromboembolic risk stratification in patients with atrial fibrillation. This score system has found widespread application among clinicians and is now deployed worldwide to guide the selection of atrial fibrillation patients for oral anticoagulation. Besides patients with atrial fibrillation, the CHA_2DS_2VASc score has proved useful for stroke and thromboembolic risk stratification in various other groups of patients; however, the validity of the CHA_2DS_2VASc score has only been sparsely investigated in patients with ischemic stroke and no atrial fibrillation.

The aim of study 1 was to investigate how the CHA_2DS_2VASc score predicts the risk of ischemic stroke recurrence in a nationwide cohort of patients with incident ischemic stroke and no atrial fibrillation, and to compare the CHA_2DS_2VASc score with the more specific Essen Stroke Risk Score. We found an association between an increasing CHA_2DS_2VASc score and Essen Stroke Risk Score and the risk of ischemic stroke recurrence. The discriminatory performance of both scores was modest with C-statistics about 0.55.

To investigate the predictive value of radiological variables of cerebral small vessel disease and the risk of ischemic stroke recurrence, and to investigate the potential of these variables for enhancing the performance of the CHA_2DS_2VASc score and the Essen Stroke Risk Score, we identified a local cohort of patients with incident ischemic stroke, no atrial fibrillation, and an available brain MRI scan. On the MRI scans, we rated the severity of white matter hyperintensities and we counted the number of silent lacunes.

In Study 2, we investigated the association between white matter hyperintensities and the risk of ischemic stroke recurrence in patients without atrial fibrillation. Furthermore, we investigated the potential for enhancing the performance of the CHA_2DS_2VASc score and the Essen Stroke Risk Score with information on white matter hyperintensities. We found a statistically significant association between the severity of white matter hyperintensities and the risk of ischemic stroke recurrence. By adding one point for moderate-to-severe white matter hyperintensities to the CHA_2DS_2VASc score and the Essen Stroke Risk Score, we found a statistically significant increase in the C-statistic of both scores. The score based on white matter hyperintensities alone had the numerically highest C-statistic, though this was not significantly better than the C-statistic of the clinical scores.

In Study 3, we investigated the association between silent lacunes and the risk of ischemic stroke recurrence. We found that patients with multiple (two or more) silent lacunes had an increased risk of a recurrent ischemic stroke compared with patients with no silent lacunes. The addition of one point for multiple silent lacunes did not enhance the discriminatory performance of the CHA_2DS_2VASc score and the Essen Stroke Risk Score in ischemic stroke recurrence prediction.

To summarize, we found an association between an increasing CHA_2DS_2VASc score and Essen Stroke Risk Score and the risk of recurrent ischemic stroke in patients with incident ischemic stroke and no atrial fibrillation. Both of the investigated risk scores showed modest discriminatory performance, and routine clinical application in stroke recurrence prediction is not recommended. For the first time, we show that the discriminatory performance of the CHA_2DS_2VASc score and the Essen Stroke Risk Score can be enhanced by adding one point for moderate-to-severe white matter hyperintensities, and that white matter hyperintensities alone show better, though insignificant, discriminatory performance than the clinical scores in the prediction of ischemic stroke recurrence. Future studies should focus on the development of stroke risk scores based on neuroimaging variables like white matter hyperintensities, possibly in combination with clinical variables.

DANSK RESUME

Apopleksi rammer årligt næsten 11.000 danskere. På verdensplan er apopleksi den næsthyppigste årsag til død og den hyppigste årsag til erhvervet handicap.

Iskæmisk apopleksi udgør cirka 85% af alle tilfælde af apopleksi. Den kumulerede 5-årsrisiko for ny apopleksi efter den første iskæmiske apopleksi angives i visse studier at være helt op til 32%. Tiltag med henblik på forebyggelse af ny apopleksi er derfor en vigtig del af den efterfølgende medicinske behandling. Risikoen for recidiv varierer dog mellem patienter, således at risikoen for nogle grupper af patienter er væsentligt højere og for andre grupper væsentligt lavere end den gennemsnitlige risiko. På nuværende tidspunkt er den medicinske behandling i vid udstrækning den samme for alle patienter med iskæmisk apopleksi uden atrieflimmer, men på sigt kunne valide værktøjer til risikostratifikation af patienter med iskæmisk apopleksi uden atrieflimmer bidrage til en mere individualiseret behandling med optimal balance mellem risici og fordele for den enkelte.

CHA_2DS_2VASc-scoren er en risikoscore udviklet med henblik på stratifikation af den individuelle risiko for apopleksi og systemisk tromboembolisme hos patienter med atrieflimmer. CHA_2DS_2VASc-scoren har opnået stor udbredelse og anvendes nu som hjælp til udvælgelse af patienter til oral antikoagulation over store dele af verden. Desuden har den vist sig brugbar til risikostratifikation i et bredt udsnit af andre patientkategorier, men har kun i begrænset omfang været undersøgt hos patienter med iskæmisk apopleksi uden atrieflimmer.

Formålet med studie 1 var at undersøge anvendeligheden af CHA_2DS_2VASc-scoren til prædiktion af risikoen for recidiv af apopleksi i en landsdækkende kohorte af patienter med førstegangs iskæmisk apopleksi uden atrieflimmer, og sammenligne CHA_2DS_2VASc-scoren med Essen Stroke Risk Score. Vi fandt en sammenhæng mellem stigende CHA_2DS_2VASc-score og Essen Stroke Risk Score og risikoen for recidiv af iskæmisk apopleksi. Diskriminationsevnen af begge scores i forhold til ny iskæmisk apopleksi var lav med *C-statistics* omkring 0.55.

Med henblik på at undersøge den prædiktive værdi af radiologiske variable i forhold til ny apopleksi og disses værdi i forhold til at optimere CHA_2DS_2VASc-scoren identificerede vi en lokal kohorte af patienter med førstegangs iskæmisk apopleksi uden atrieflimmer, som havde undergået MR scanning af hjernen. På MR scanningerne beskrev vi sværhedsgraden af småkarssygdom i form af *white matter hyperintensities* og klinisk stumme lakuner.

I studie 2 undersøgte vi sammenhængen mellem *white matter hyperintensities* på MR og risikoen for ny apopleksi samt hvorvidt tillæg af ét point til CHA_2DS_2VASc-

scoren og Essen Stroke Risk Score for moderate til svære *white matter hyperintensities* kunne øge diskriminationsevnen af disse kliniske scores. Vi fandt en stigende risiko for recidiv af iskæmisk apopleksi med stigende sværhedsgrad af *white matter hyperintensities*. Ved at lægge ét point til CHA_2DS_2VASc scoren og Essen Stroke Risk Score for moderate til svære *white matter hyperintensities* fandt vi en statistisk signifikant øget diskriminationsevne af begge scores, vurderet ved *C-statistics*. Scoren baseret udelukkende på *white matter hyperintensities* havde den bedste diskriminationsevne af alle scores, omend den dog ikke var statistisk signifikant bedre end de kliniske scores.

I studie 3 undersøgte vi sammenhængen mellem klinisk stumme cerebrale lakuner og risikoen for recidiv af iskæmisk apopleksi. Vi fandt, at patienter med multiple (to eller flere) stumme lakuner på MR havde en øget risiko for recidiv af iskæmisk apopleksi sammenlignet med patienter uden stumme lakuner. Tillæg af ét point for tilstedeværelse af multiple stumme lakuner på MR førte ikke til bedre diskriminationsevne af CHA_2DS_2VASc scoren og Essen Stroke Risk Score.

Sammenfattende fandt vi en sammenhæng mellem stigende CHA_2DS_2VASc score og Essen Stroke Risk Score og øget risiko for recidiv af iskæmisk apopleksi hos patienter med førstegangs iskæmisk apopleksi uden atrieflimmer. Begge scores havde dog en lav diskriminationsevne, og klinisk anvendelse af de to scores i denne sammenhæng kan ikke anbefales. For første gang har vi vist, at diskriminationsevnen af CHA_2DS_2VASc-scoren og Essen Stroke Risk Score kan øges ved at tillægge point for *white matter hyperintensities*, og at *white matter hyperintensities* alene har bedre, men dog ikke signifikant bedre, diskriminationsevne end CHA_2DS_2VASc scoren og Essen Stroke Risk Score i prædiktionen af recidiv af iskæmisk apopleksi. Fremtidige studier bør fokusere på at udvikle anvendeligheden af scores baseret på *white matter hyperintensities*, eventuelt i kombination med kliniske variable.

TABLE OF CONTENTS

CHAPTER 1. INTRODUCTION

The themes of this dissertation are ischemic stroke and risk stratification in non-atrial fibrillation (AF) ischemic stroke patients. The central topic is the assessment of the risk of recurrent ischemic stroke. This topic is explored through three sub-topics: 1) Evaluation of the performance of existing risk score schemes, mainly the CHA_2DS_2VASc (congestive heart failure, hypertension, age $\geq$ 75 years, diabetes mellitus, previous stroke or TIA, vascular disease, age 65-74 years, and sex class (female)) score[1], in the prediction of recurrent ischemic stroke. 2) The association of radiological signs of cerebral small vessel disease and the risk of recurrent ischemic stroke. 3) The potential of combining existing clinical risk score schemes with information on small vessel disease to enhance the performance of the existing score schemes in stroke recurrence risk prediction. As an introduction to the following chapters on the specific studies, I present some basic aspects of stroke and cerebral small vessel disease, and introduce the CHA_2DS_2VASc score.

1.1. STROKE

Stroke is defined by the World Health Organization (WHO) as "rapidly developed clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin".[2] This definition covers very different, common diseases of vascular origin: brain infarcts, intracerebral hemorrhages, and subarachnoid hemorrhages, besides some more rare conditions.[2] Even though this definition of stroke, which was introduced in 1970, is obsolete mainly because of the advent of modern neuroimaging techniques, it still very well captures the clinical appearance of a stroke: sudden symptoms that without warning deprives the victim of his physical and/or mental independency, or even life. The consequences are enormous for the individual and for the society.

A recent attempt to revise the stroke definition refers to ischemic stroke as "an episode of neurological dysfunction with evidence of central nervous system infarction."[3] The evidence of infarction will generally be based on neuroimaging. The same document gives an analogous definition of hemorrhagic stroke: "neurological dysfunction with evidence of intracerebral hemorrhage." In Danish, the word "apopleksi" usually covers ischemic and hemorrhagic strokes together, but does not include subarachnoid hemorrhage. In the present dissertation, I use "stroke" as a collective term to cover ischemic and hemorrhagic strokes. Where appropriate, stroke will be categorized as ischemic or hemorrhagic.

The definition of transient ischemic attack (TIA) is also under revision. The classic definition formulated in 1975[4] did not take imaging findings into account. In the current Danish guidelines, TIA is diagnosed in case of symptoms lasting less than 24

hours and no evidence of CNS infarction.[5] Otherwise, the attack should be considered an instance of (ischemic) stroke.

Epidemiology

Stroke is a very common disease. Worldwide, stroke is the second leading cause of death and the most frequent cause of acquired disability.[6] Over the last four decades, the incidence rate of stroke has decreased in the high-income countries, whereas the opposite trend is seen in the low- to middle-income countries.[7] In Denmark in 2014, almost 11,000 cases of stroke occurred in the population aged >18 years; of these, approximately 85% were of ischemic origin. In addition, about 4,200 cases of TIA occurred. The overall incidence rate of stroke was 2.4 per 1,000 person-years, and the overall incidence rate has been slightly decreasing during the past decade.[8] The thirty-day mortality was 7% in ischemic stroke and 26% in hemorrhagic stroke.[9] In Denmark, an estimated 30,000-40,000 people live with disabilities after a stroke.[5]

Ischemic Stroke

Ischemic stroke is a very heterogeneous disease. Its causes are many, counting age-related conditions, heart diseases, genetic causes, inflammatory and immunologic diseases, among many others. A few causes are very common, whereas the majority of causes are relatively rare. In every patient, an individualized diagnostic workup should be instituted to identify the underlying cause of the stroke. Correct identification of the cause has important implications for treatment and prognosis.[5,10]

Ischemic stroke can be subtyped according to various classification systems.[10] The most widely applied classification system is The Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification, introduced in 1993.[11] This system is an etiologically based classification system with five categories: large-artery atherosclerosis, cardioembolism, small vessel occlusion, stroke of other determined cause, and stroke of undetermined cause. This classification system is far from perfect, and the frequency of the different categories may vary with the persistence displayed during diagnostic workup.[10] Despite its shortcomings, the TOAST classification contributes to an understanding of the heterogeneity of stroke pathophysiology and can be used for comparison of the relative frequencies of the defined causes.

In recent European studies of the distribution of stroke subtypes according to the TOAST classification, 11-36% were due to large-artery atherosclerosis, 24-31% were due to cardioembolism, 23-31% were caused by small vessel occlusion, and 2-26% were of undetermined or other causes.[12–15] AF is quantitatively the most important cause of cardioembolic stroke.[16]

Management of Ischemic Stroke

The acute management of stroke has evolved dramatically over the past few years. Intravenous thrombolytic therapy of acute stroke with alteplase (recombinant tissue-type plasminogen activator, tPA)[17,18] was approved in Denmark in 2003; and in 2015, mechanical thrombectomy became standard care for patients with large-vessel occlusions.[19–21] Unfortunately, only 15% of the stroke patients are offered these new treatments,[9] primarily due to time delays in hospitalization and individual contraindications to the interventions. Hence, despite these landmarks in acute stroke care, secondary prevention remains the cornerstone in the treatment of the majority of ischemic stroke patients. Secondary prevention consists of medications, surgical interventions, management of comorbidities, and lifestyle modifications.[22]

The primary goal of secondary prevention is to prevent stroke recurrence and other related diseases. In AF patients, oral anticoagulant therapy has proved effective in the prevention of stroke and thromboembolism.[23–26] Treatment decisions are guided by risk stratification according to the CHA_2DS_2VASc score, and this score is now an integrated part of clinical management of AF patients.[27,28] In non-AF stroke patients, no single risk score scheme has gained broad application, and only a few of the existing score schemes have been developed specifically for patients with non-cardioembolic stroke.[29,30] Broadly speaking, secondary preventive medical treatment in non-AF stroke patients is the same irrespective of the underlying cause and the patient's individual characteristics (apart from some uncommon causes of stroke).[5,31] Validation of risk assessment tools for this group of patients may therefore be the first step towards a differentiated and individualized treatment strategy that may lead to an optimized risk-benefit ratio for all patients.

1.2. CEREBRAL SMALL VESSEL DISEASE

Cerebral small vessel disease refers to a group of diseases affecting the small vessels of the brain. The quantitatively most important etiology of small vessel disease is related to age and vascular risk factors. In addition, amyloid angiopathy is relatively common. Other more rare causes are genetic diseases and iatrogenic conditions, for example post-radiation small vessel disease.[32] Though the disorders of the vessels and the resulting parenchymal changes are pathologically defined entities strictly speaking, and thereby only very rarely accessible for direct study, neuroimaging characteristics are established in vivo surrogate markers of small vessel disease.[33]

The conventional magnetic resonance imaging (MRI) markers of cerebral small vessel disease are white matter hyperintensities, lacunes, cerebral microbleeds, and enlarged perivascular spaces.[34–37] Leukoaraiosis and age-related cerebral white matter changes are synonymous with white matter hyperintensities.[38] In the existing literature, a predominance of studies focus on white matter hyperintensities and lacunes because these changes are visible on computed tomography (CT). However,

with the wider access to MRI, more attention is now being paid to microbleeds and enlarged perivascular spaces.

Prevalence

Beyond doubt, the prevalence of cerebral small vessel disease is age-dependent. In the population-based Rotterdam Scan Study, the prevalence of moderate-to-severe white matter hyperintensities was 11% in those aged 65-69 years and rose to 54% in those aged 80-84 years.[39] In the same study, the prevalence of silent cerebral infarcts (of which 95% were lacunes) was 8% in those aged 60-64 years and 35% in the age group above 85 years.[40] The prevalence of cerebral microbleeds was 17.8% in the group aged 60-69 years and 38.3% in those above 80 years.[41]

In the review of studies on radiologically assessed cerebral small vessel disease, it is important to notice that numerous rating scales exist for the assessment of white matter hyperintensities.[42] These scales may differ with respect to the areas of the brain included in the rating. Some are visually based, while others rely on computerized volumetric measurements.[43] Similarly, differences in imaging protocols, equipment, and definitions may hamper direct comparison between studies of prevalence and significance of the imaging parameters described above.

Clinical Consequences

Cerebral small vessel disease is associated with a number of serious clinical symptoms: cognitive decline, dementia, gait disturbances, and urinary incontinence.[44,45] Although these symptoms are generally accepted consequences of small vessel disease, the correlation between the severity of the radiological changes and the clinical disability is more ambiguous. Widespread small vessel disease may apparently be clinically silent and, on the other hand, patients with obvious clinical symptoms consistent with cerebral small vessel disease may harbor only mild changes on neuroimaging.[44,45] Besides the aforementioned symptoms, small vessel disease has also been linked to an increased risk of recurrent ischemic stroke. Neuroimaging signs of small vessel disease may therefore have potential as predictors of stroke, in isolation or in the combination with existing risk scores such as the CHA_2DS_2VASc score.

1.3. THE CHA_2DS_2VASC SCORE

Risk prediction is the estimation of a person's risk or probability of experiencing a certain event over a specific time. The event could be a disease, death, or effect of a treatment. Risk stratification is an approach that divides patients into risk groups according to their individual risk, and stratification may be accomplished using risk-score schemes, for instance the CHA_2DS_2VASc score. Hence, risk stratification is a tool to predict the prognosis of the patient.[46,47]

The use of risk stratification for prognostic purposes may serve several additional purposes. First, the prognosis is of particular interest to the patient and is an important element in the counseling of the patient and the relatives. Documentation of a particular high risk may help motivate the patient to accept risk-factor-modifying lifestyle behavior. Furthermore, risk stratification may guide treatment decisions and can be used in research to select patients for a study or to allocate patients to different treatments.[46]

Risk stratification can be based on a variety of different predictors or variables. Clinical variables are probably the most commonly included predictors in risk-score schemes, and the CHA_2DS_2VASc score is an example of an exclusively clinically based risk score. The CHA_2DS_2VASc score is a refinement of the simpler $CHADS_2$ (heart failure, hypertension, age $\geq$ 75 years, diabetes mellitus, previous stroke or TIA) score[48] and it was developed specifically for the stratification of stroke and thromboembolic risk within 1 year in AF patients. Since its introduction, the CHA_2DS_2VASc score has been validated in various cohorts[49,50] and has proven applicable for stroke risk prediction in various groups of patients without AF, including patients with ischemic stroke,[51] coronary heart disease,[52] patients undergoing coronary artery bypass,[53,54] and patients with congestive heart failure.[55] In addition, the CHA_2DS_2VASc score may predict the risk of new-onset AF[56] as well as the risk of stroke and thromboembolism in the general population.[57] Recently, the CHA_2DS_2VASc score showed promise of enhanced performance when combined with information on chronic kidney disease.[58] Hence, the CHA_2DS_2VASc score seems to be applicable in various different patient categories and may have the potential to become an even better predictor if combined with selected new variables.

Summary

Ischemic stroke is a common disease with great impact on the individual and on society. Only few risk stratification studies have focused specifically on patients with non-AF related ischemic stroke. Cerebral small vessel disease affects the small, deep vessels of the brain and can be visualized in vivo on standard neuroimaging protocols. Neuroimaging signs of cerebral small vessel disease have been associated with an increased risk of recurrent ischemic stroke and these signs may serve as predictors of stroke risk. The CHA_2DS_2VASc score is a clinically based risk score scheme with a promising potential to improve risk stratification in various patient categories and to become an even better predictor if combined with other, new predictors.

CHAPTER 2. AIMS

The aims of this dissertation are:

1. To evaluate how the CHA_2DS_2VASc score predicts ischemic stroke recurrence, death, and cardiovascular events in a nationwide cohort of non-AF patients with incident ischemic stroke and to compare its performance in this respect with that of the more specific Essen Stroke Risk Score.

2. To investigate the association of white matter hyperintensities with the risk of ischemic stroke recurrence, death, and cardiovascular events, and to investigate whether information on white matter hyperintensities can enhance the predictive performance of the CHA_2DS_2VASc score and the Essen Stroke Risk Score.

3. To investigate the association of silent lacunes with the risk of ischemic stroke recurrence, death, and cardiovascular events, and to investigate whether information on silent lacunes can enhance the predictive performance of the CHA_2DS_2VASc score and the Essen Stroke Risk Score.

CHAPTER 3. CLINICAL RISK SCORES AND RECURRENT ISCHEMIC STROKE

As outlined in Chapter 1, risk stratification in AF patients and in stroke patients with AF is an integrated part of clinical practice. The individual risk assessment in stroke patients without AF has been studied much less intensively although this group constitutes more than three fourths of all ischemic stroke patients. Attempts to expand knowledge in this important area are of major clinical interest and may benefit patients in the future.

Study 1 aimed to evaluate the performance of the CHA_2DS_2VASc score in the prediction of recurrent ischemic stroke, death, and cardiovascular events in a cohort of non-AF patients with incident ischemic stroke. We compared the performance of the CHA_2DS_2VASc score with that of the Essen Stroke Risk Score.[59,60] The latter is a point-based risk score scheme developed specifically for prediction of recurrent ischemic stroke within 1 year from the index stroke. The concept of this model is very similar to that of the CHA_2DS_2VASc score, even if they differ slightly in the included variables (The Essen Stroke Risk Score is shown in Appendix A).

3.1. RISK OF RECURRENT ISCHEMIC STROKE

The cumulative risk of stroke recurrence varies among cohorts.[61] Studies reporting on the cumulative risk of stroke recurrence differ in their inclusion criteria: some included only ischemic stroke, whereas others included all types of stroke.[61] In a meta-analysis, Mohan et al. found no significant differences in recurrence risk between studies reporting on ischemic stroke only versus those reporting on all types of stroke.[61] In the following, I focus on clinically relevant time perspectives and include studies on all types of stroke.

In the derivation cohort of the Recurrence Risk Estimator at 90 days (RRE-90)[62] and in the Oxford Vascular Study[63], the cumulative risk of recurrent ischemic stroke varied from 2.6% to 11.5% at 7 days and from 6.0% to 18.5% at 90 days. The cumulative risk of stroke recurrence at 1 year varied from 7.1% in the South London Stroke Registry[64] to 16.0% in the Perth Community Stroke Study.[65] Corresponding values at 5 years in the same two cohorts were 16.2% and 32.0%, respectively, and at 10 years 24.5% and 43.0%, respectively.

In a meta-analysis, subdivision according to the TOAST classification showed that the risk of ischemic stroke recurrence was highest for large-artery atherosclerosis and lowest for small vessel stroke: 19.2% versus 3.4% at 3 months.[66] The recurrence risk at 3 month after cardioembolic stroke was 11.9%.

In The South London Stroke Register,[67] the incidence rate of stroke recurrence among patients where ischemic stroke was the index event was 7.8% during the first year of follow-up, whereas the incidence rate was only 2.5% during the fifth year of follow-up. Similar results were found in the Life Long After Cerebral ischemia (LiLAC) study cohort.[68] In a Finnish study of young stroke patients (15-49 years)[69], the incidence rate of stroke recurrence was 3.0% during the first year, whereas the yearly recurrence rate declined to about 2% the following years.

Mohan et al. performed a meta-analysis of 13 studies reporting on the cumulative risk of stroke recurrence.[61] The included studies covered a period of 50 years. In their analyses, they observed a trend of decreasing stroke recurrence risk in the more recent studies. This is in accordance with a Swedish study that reported a hazard ratio of stroke recurrence of 0.64 (95% CI 0.52-0.78) for patients included in the cohort in 2004-2008 versus those included in 1995-1998.[70]

In conclusion, the risk of stroke recurrence is considerable. During the first 5 years, the cumulative risk of recurrence varies between 16% and 32%,[64,65] and large-artery atherosclerosis-related stroke may carry the highest risk of recurrence. The rate of recurrence is highest in the period immediately after the stroke and declines in the years following the index event. Overall, the risk of stroke recurrence seems to have decreased during the past 20 years.

3.2. RISK SCORE SCHEMES IN ISCHEMIC STROKE

Existing Models

There are several risk score schemes and models for predicting ischemic stroke. Most famous is probably the Framingham risk score which estimates the risk of stroke within 10 years in the general population.[71] However, the Framingham risk score was developed for estimating the risk of incident stroke in the general population. Yet, from the neurologist's perspective, the risk of recurrent stroke is most often the relevant question.

The table in Appendix B gives an overview of various multivariable risk prediction models derived from TIA and stroke cohorts and aimed for estimating the risk of a recurrent ischemic stroke or, in the TIA patients, the risk of a subsequent stroke. The table includes only models with specific assessment of stroke recurrence risk. The table was modified from Thompson et al.[72] and has been extended with models not fulfilling their inclusion criteria as well as models derived from TIA cohorts.

The models vary in terms of the number of included variables and the complexity of these variables and, thereby, in the complexity of the different model. The most frequently included variables are age, history of TIA or stroke, hypertension, and diabetes.[72] Some models included variables based on advanced neuroimaging or

electrocardiographic (ECG) characteristics. Besides varying in terms of the included variables and overall complexity, the models also vary considerably in their time perspective; some estimate stroke risk within 2 days[73], whereas others estimate stroke recurrence risk up to 10 years after the index event.[68]

Some of the models are point-based, whereas others are based on regression equations. In point-based models, one or more points are added for each variable present. A major advantages of these models are the simplicity of calculating the individual score and that the ability to tabulate the associated risk in a simple table. The most significant disadvantage is that information is lost when a regression coefficient is reduced to a binary variable (present/not present).[47] In the models with more advanced regression equations, a computer is needed to calculate the risk; however, today this can easily be accomplished with a web-based model or a mobile app.[72]

Evaluation and Comparison of Prediction Models

Prediction models must be evaluated to quantify and document how well they predict the outcome. In point-based models such as the CHA_2DS_2VASc score and the Essen Stroke Risk Score, tabulation of the observed risk or incidence rates stratified on the score is a simple way to obtain an overview of the applicability of the prediction model. However, more thorough methods of evaluation are necessary, for example to determine the discriminative performance. The discriminative performance of a prediction model is its ability to discriminate between those with and those without the outcome of interest. A commonly applied statistical measure of discrimination is the C-statistic. For binary outcomes, the C-statistic is calculated as the area under the receiver operating characteristics (ROC) curve.[47] The C-statistic of a model is the probability that an individual with the event of interest is assigned a higher predicted probability than an individual without the event.[74] A C-statistic of 1.0 indicates perfect discrimination, whereas a C-statistic of 0.5 indicates that the model is no better than chance in predicting the outcome.[75] The calibration of a prediction model is an assessment of the agreement between the predicted and the observed risk.[75] Most studies report measures of discrimination, whereas measures of calibration are more sporadically reported. In the studies of this dissertation, we applied the C-statistic as the primary measure of model performance. Calibration is mainly relevant in validation studies, and we did not assess calibration in our studies as, per definition, the predicted risk was identical to the observed risk. A prediction model is developed from a derivation cohort in which the variables are selected. The model should subsequently be evaluated in other cohorts to prove its external validity.[76]

Thompson et al.[72] performed a meta-analysis of validation studies in stroke cohorts and they were able to report pooled C-statistics for the Essen Stroke Risk Score and the Stroke Prognosis Instrument-II. The pooled C-statistics were 0.60 (95% confidence interval (CI) 0.59-0.62) and 0.62 (95% CI 0.60-0.64), respectively.

Among all included models in the validation studies, C-statistics varied between 0.50 and 0.75. Of the 27 C-statistic values reported, only two were above 0.70. Both of these were in studies of the Recurrence Risk Estimator at 90 days (RRE-90).[77] In comparison, the CHA_2DS_2VASc score (on the composite thromboembolic endpoint) had C-statistics of 0.61 (95% CI 0.51-0.70) in the derivation cohort[1] and 0.66 (95% CI 0.63-0.69) and 0.67 (95% CI 0.67-0.68), respectively, in two subsequent validation studies.[49,50]

3.3. STUDY 1

Results

Study 1 was a register-based cohort study on patients with incident ischemic stroke and no AF. Patients who suffered incident ischemic stroke in the period 2003-2012 were identified in the Danish Stroke Registry, and data were linked with information from the Danish National Patient Registry, The National Prescription Registry, and The Danish Civil Registration System. The outcomes were recurrent ischemic stroke, death, and cardiovascular events.

The study comprised 42,182 patients with a median age of 70.1 (interquartile range (IQR) 19.3) years. Based on the information in the registries, we calculated the CHA_2DS_2VASc score and the Essen Stroke Risk Score. Patients were followed up until ischemic stroke recurrence, or death, whichever came first.

The cumulative risk and the incidence rates of all three outcomes increased with increasing values of the risk scores at both 1 and 5 years. The figures in Appendix C

Table 1. C-statistics for the CHA_2DS_2VASc score and the Essen Stroke Risk Score.

Endpoint		CHA_2DS_2VASc score	Essen Stroke Risk Score
Recurrent ischemic stroke	1-year	0.52 (0.51-0.53)	0.54 (0.53-0.55)
	5-year	0.54 (0.53-0.55)	0.56 (0.55-0.57)
Death	1-year	0.68 (0.67-0.68)	0.65 (0.64-0.66)
	5-year	0.68 (0.68-0.69)	0.66 (0.66-0.67)
Cardiovascular events	1-year	0.53 (0.52-0.54)	0.55 (0.54-0.56)
	5-year	0.55 (0.54-0.56)	0.57 (0.57-0.58)

Data are C-statistics (95% CI).

show the stratified cumulative risk of recurrent ischemic stroke. Similarly, the Cox proportional hazard ratios rose with increasing values of the risk scores. The C-statistics of the discriminative performance of the scores are shown in Table 1. The 1-year negative predictive value for recurrent ischemic stroke for a CHA_2DS_2VASc score of 2 was 0.94 (95% CI 0.94-0.95), and the corresponding value for an Essen Stroke Risk Score of 0 was 0.95 (95% CI 0.94-0.96).

Study-Specific Methodological Considerations on Study 1

In the study cohort of Study 1, 25.3% of the patients died during follow-up. Death precludes the occurrence of the event of interest; in this case recurrent ischemic stroke and cardiovascular events. Therefore, death is considered to be a competing risk, and this should be taken into account in the calculation of the risk of the outcome of interest.[78] In the conventional Kaplan-Meier approach, censoring is non-informative. However, death is tantamount to informative censoring: those patients who die are no longer at risk.[79] The significance of competing risks depends on the duration of follow-up and the frailty of the study population. Short periods of follow-up and low mortality in a study cohort decrease the extent to which competing risks affect the estimates. Without competing risks, there is a one-to-one correspondence between the rate and the risk for the outcome of interest. In case of competing risks, this one-to-one relation between the cause-specific (for the outcome of interest) rate and the risk no longer exists.[80] The result is a biased estimate of the cumulative incidence based on the Kaplan-Meier estimator. Another consequence is that the effect of the covariates may differ in the cause-specific hazard function and the cumulative incidence function.[79–81] Thus, covariates or predictors selected on the basis of the Cox proportional hazards do not necessarily contribute to the cumulative incidence with the same weight as observed in the regression model. Based on these considerations, we calculated the cumulative risk and the C-statistic, taking into account the competing risk of death.

We identified the study cohort in the Danish Stroke Registry although the cohort could also have been identified in the Danish National Registry of Patients. A recent study investigated and compared the validity of the stroke diagnoses of these two registries.[82] The sensitivity of the stroke diagnoses in the Danish Stroke Registry was 91-97%, and the positive predictive value was 90%. In the Danish National Registry of Patients, the sensitivity was 58-79% and the positive predictive value was 79%. We drew samples of patients with incident ischemic stroke and no AF in the period 2003-2012 from both registries. The sample from the Danish National Registry of Patients comprised about 62,000 patients, whereas the sample from the Danish Stroke Registry comprised about 42,000 patients. In the light of these numbers and the above cited results on sensitivity and positive predictive values, we chose the Danish Stroke Registry as the source of the study population.

Discussion

As seen from the table in Appendix B, the factors included in the CHA_2DS_2VASc score are not very different from the factors in many of the stroke-specific models. Hence, from a theoretic point of view, the CHA_2DS_2VASc score is likely to be predictive of the risk of ischemic stroke recurrence among stroke patients.

From a clinical point of view, the absolute risk of the outcome will usually be the most relevant measure to guide treatment decisions. The 1-year cumulative risks of stroke recurrence were about 2.5% versus 4.1% for a CHA_2DS_2VASc score of 2 versus ≥7, respectively (figures in Appendix C). While the Cox proportional hazard analyses showed that a CHA_2DS_2VASc score ≥7 was associated with a statistically significantly higher relative risk of ischemic stroke recurrence, it may be questioned whether this difference is also of clinical significance. Compared with the 1-year cumulative risks of death ranging from about 2.5% to 22% for a CHA_2DS_2VASc score of 2 versus ≥7, respectively, the differences in stroke recurrence risk are only minor. The differences in the 5-year cumulative risks were somewhat larger: the risk of recurrent ischemic stroke ranged from about 7% to 10%. In comparison, in a Swedish registry study, the annual stroke rate in non-anticoagulated AF patients varied from 0.2% to 12.2% for a CHA_2DS_2VASc score of 0 versus 9.[50] In the light of these numbers, the performance and the clinical utility of the CHA_2DS_2VASc score was not very convincing in our cohort.

The Essen Stroke Risk Score was a better tool for determining the risk of recurrent ischemic stroke. The 1-year cumulative risk ranged from about 2% to 4% whereas the 5-year risk ranged from about 5% to 11% for a score of 0 versus a score of ≥5, respectively; and the corresponding hazard ratios for a score of ≥5 were higher: 2.30 (95% CI 1.64-3.22) (1-year) and 2.81 (95% CI 2.22-3.54) (5-year). With high-risk patients having more than twice the risk of stroke recurrence, the results of the Essen Stroke Risk Score are of greater clinical relevance. However, it is debatable whether we identified a group that had a particularly high risk. Compared with the stroke risk in the AF patients,[50] the baseline stroke risk in our patients is considerable. In other words, all stroke patients are high-risk patients, at least when stratified by these two clinical scores.

As expected, the incidence rates of cardiovascular events were higher than the incidence rates of stroke recurrence, and the hazard ratios were also somewhat higher. The highest incidence rates were observed for the outcome of death. Overall, our findings are in agreement with those of a previous study from the Athens Stroke Registry.[51] In this study, Ntaios et al. investigated the association of the $CHADS_2$ and the CHA_2DS_2VASc score with the risk of recurrent ischemic stroke, death, and cardiovascular events in a minor non-AF stroke cohort.[51] They stratified patients into low, intermediate and high-risk groups ("prestroke" $CHADS_2$ and CHA_2DS_2VASc scores of 0, 1, and ≥2 respectively). They found that in the Cox proportional hazard

analyses, the risk of the outcomes increased with increasing risk scores, and the highest hazard ratio was observed for death.

In our study, the C-statistics of the CHA_2DS_2VASc score for recurrent ischemic stroke and cardiovascular events were comparable and low, whereas the score performed reasonably well for prediction of death with C-statistics around 0.68. In another study from the Athens Stroke Registry, Ntaios et al. reported C-statistics of both the $CHADS_2$ and the CHA_2DS_2VASc scores of 0.56 for the prediction of ischemic stroke recurrence in non-AF patients after a median follow-up of 30 months.[83]

Importantly, female sex is included in the CHA_2DS_2VASc score, but not in the Essen Stroke Risk Score. In the derivation cohort of the CHA_2DS_2VASc score[1], female sex was associated with an odds ratio (OR) of thromboembolic events of 2.53 (95% CI 1.08-5.92). In our study, we performed Cox proportional hazard analysis on the individual factors of the scores. The 1-year hazard ratio of female sex in recurrent ischemic stroke was 0.87 (95% CI 0.78-0.98). Hence, in our cohort, female sex actually seemed to be protective regarding the risk of ischemic stroke recurrence. The issue of female sex as a risk factor was also raised in a recent Danish study on thromboembolism in patients with incident AF.[84] In this register-based study, female sex was associated with a hazard ratio of 0.77 (95% CI 0.55-1.13). Apart from female sex, all other factors included in the CHA_2DS_2VASc score and the Essen Stroke Risk Score were positively associated with ischemic stroke recurrence.

The CHA_2DS_2VASc score was strongly associated with death. This is not surprising considering the factors comprised in the score: age is a very strong risk factor for death. Furthermore, congestive heart failure and vascular disease are also associated with high mortality.[85,86] In the prediction of death, the C-statistic was higher for the CHA_2DS_2VASc score than for the Essen Stroke Risk Score. One possible explanation for this is found in the risk factor "smoking", which is included in the Essen Stroke Risk Score. In the Cox proportional hazard analyses, smoking was associated with a hazard ratio of death of 0.59 (95% CI 0.56-0.63). The apparently lower mortality among smokers is also known from patients with coronary heart disease, where it is described as the "smoker's paradox".[87] Our estimate was not adjusted for age, sex and comorbidities; however, in several studies of patients with acute myocardial infarction, this could not fully explain the paradox.[87] It has been proposed that smokers may suffer more severe myocardial infarctions (and possibly, more severe ischemic strokes) and thereby have a higher pre-hospital mortality than non-smokers; however, this issue remains unsolved.[88,89]

Conclusions on Study 1

The CHA_2DS_2VASc score showed low discriminatory performance in the prediction of recurrent ischemic stroke and cardiovascular events. In terms of absolute risks, the

differences over the strata were of limited clinical significance. The Essen Stroke Risk Score performed marginally better than the CHA_2DS_2VASc score. Non-AF ischemic stroke patients have a high baseline risk of stroke recurrence, and the clinical variables included in the CHA_2DS_2VASc score and the Essen Stroke Risk Score showed only limited ability to differentiate between low-risk and high-risk patients. The results warrant caution before applying the scores in clinical practice, in particular for the endpoints of recurrent ischemic stroke and cardiovascular events.

CHAPTER 4. WHITE MATTER HYPERINTENSITIES AND RECURRENT ISCHEMIC STROKE

As shown in Study 1 and discussed in the previous chapter, the discriminatory performance of the CHA_2DS_2VASc score and the Essen Stroke Risk Score in the prediction of recurrent ischemic stroke was modest, and the absolute risks and hazard ratios varied only within a narrow interval. Improvement of the predictive accuracy of these risk scores will enhance their clinical utility, and the use of imaging markers of cerebral small vessel disease may be appropriate for this purpose. In the following sections, I will review the existing literature on the prognosis of white matter hyperintensities, look into aspects of how prediction models may be improved, and, finally, present and discuss the results of Study 2.

4.1. WHITE MATTER HYPERINTENSITIES AND PROGNOSIS

Ischemic Stroke

In the general population, cerebral white matter hyperintensities are a risk factor for future ischemic stroke. This finding has been replicated in several studies.[45,90–94] In contrast, the prognostic significance of white matter hyperintensities in patients with symptomatic ischemic cerebrovascular disease is been more disputed. Table 2 gives an overview of studies on white matter hyperintensities and the risk of recurrent stroke.

The majority of the studies find that white matter hyperintensities are associated with the risk of recurrent stroke. Interestingly, this seems to apply to the short-term and the medium-term prognosis, but the association is vaguer in the very long-term prognosis. Melkas et al.[95] followed 320 patients for up to 12 years. They reported an increased risk of ischemic stroke recurrence in patients with severe white matter hyperintensities after 5 years of follow-up. However, this effect was lost after 12 years of follow-up. Putaala et al.[96] followed a cohort of young ischemic stroke patients for a mean of 8.7 years and reported no association between white matter hyperintensities and the risk of ischemic stroke recurrence. Importantly, the mean age of this cohort was only 40.0 years; and therefore this association may not be directly comparable to the associations reported in the other studies. However, in the LiLAC study cohort,[68] white matter hyperintensities were associated with an increased risk of stroke recurrence after a mean follow-up of 10.1 years (HR 1.64 (95% CI 1.28-2.11)) in patients with TIA and minor stroke.

Table 2. Studies on white matter hyperintensities and recurrent stroke.

Study	N; age; imaging modality	Main findings
Miyao (1992)[97]	N=215; mean age 71.3 years; CT	Patients with first-ever stroke of lacunar type. After 1, 2, and 3 years of follow-up, patients with WMH[a] showed a significantly higher cumulative incidence of stroke recurrence and death than age- and sex-matched patients without WMH.
van Swieten (1992)[98]	N=3,017; mean age 71.4/64.4 years; CT	Patients with transient ischemic attack or minor ischemic stroke. WMH were associated an increased risk stroke recurrence, HR 1.6 (95% CI 1.2-2.2).
Clavier (1994)[99]	N=178; mean age not stated; CT and MRI	Patients with symptomatic lacunar infarct. After a mean follow-up of 35 months, bivariate and multivariate analyses did not find WMH[a] to be associated with stroke recurrence.
Podgorska (2002)[100]	N=370; mean age 72/67 years; CT	Patients with ischemic and hemorrhagic (11.6%) stroke. WMH[a] were not significantly associated with increased risk of stroke recurrence after 1 year of follow-up.
Streifler (2002)[101]	N=2618; mean age not stated; CT	Patients with symptomatic carotid stenosis (retinal or cerebral ischemia). After 3 years of follow-up, widespread WMH[a] were associated with higher risk of any stroke, HR 1.6 (95% CI 1.1-2,5) and HR 2.5 (95% CI 1.6-4.0) for medically and surgically treated patients, respectively.
Hénon (2003)[102]	N=202; median age 75 years; CT	Patients with ischemic and hemorrhagic (12%) stroke. After 3 years of follow-up, WMH[a] were associated with an increased risk of stroke recurrence, RR 1.70 (95% CI 1.23-2.36) in multivariate analysis.
Appelros (2005)[103]	N=81; mean age 66.4 years; MRI	Patients with lacunar infarcts. After 5 years of follow-up, WMH were associated with the risk of stroke recurrence, OR 1.7 (95% CI: 1.2-2.7), but not significantly with mortality.
Fu (2005)[104]	N=228; mean age 50.5-75.9 years; MRI	Patients with first-ever ischemic stroke. After a mean follow-up of 23.0 months WMH were associated with an increased risk of stroke recurrence, HR 4.18 (95% CI 2.04-8.56) as well as mortality, HR 2.02 (95% CI 1.03-3.96).
van Wijk (2005)[68]	N= 2447; mean age 65 years; CT	Patients with TIA or minor stroke. After a mean follow-up of 10.1 years, WMH were associated with the risk of stroke recurrence, HR 1.64 (95% CI 1.28-2.11), as well as mortality, HR 1.33 (95% CI 1.15-1.54).
Putaala (2011)[96]	N=655; mean age 40.0 years; MRI	Patients with first-ever ischemic stroke. After a mean follow-up of 8.7 years, WMH[a] were not associated with an increased risk of stroke recurrence, HR 1.07 (95% CI 0.40-2.85). Moderate-to-severe WMH were associated with death from any cause, HR 3.43 (95% CI 1.58-7.42).
Melkas (2012)[95]	N=320; mean age 70.8 years; MRI	Patients with first-ever ischemic stroke. Severe WMH are a risk factor for recurrent ischemic stroke after 5 years of follow-up, HR 1.80 (95% CI 1.11-2.95). After 12 years of follow-up, this effect was no longer significant.

Kim (2013)[105]	N=2,378; median age 70 years; MRI	Patients with ischemic stroke. At 90 days, extensive periventricular WMH were associated with ischemic stroke recurrence, HR 1.67 (95% CI 1.11-2.51).
Kumral (2015)[106]	N=9,522; mean age 65 years; MRI	Patients with ischemic and hemorrhagic (9.3%) stroke. At 5 years, WMH were associated with increased risk of stroke recurrence in patients with index stroke caused by large-artery disease (OR 1.39 (95% CI 1.18-1.64)) and small-artery disease (OR 1.57 (95% CI 1.27-1.94)), but not in cardioembolic and "other" index stroke subtypes.
Ntaios (2015)[83]	N=1,892; median age 71.0 years; CT and MRI	Patients with first-ever ischemic stroke. After a median follow-up of 30.0 months, WMH[a] were associated with an increased risk of stroke recurrence in patients without AF (HR 1.82 (95% CI 1.31-2.51)), but not in patients with AF (HR 1.02 (95% CI 0.63-1.66)).

[a)] The authors applied the term "leukoaraiosis". Abbreviations: CT, computed tomography; WMH, white matter hyperintensities; RR, relative risk; CI, confidence interval; MRI, magnetic resonance imaging; HR, hazard ratio; OR, odds ratio; AF, atrial fibrillation.

Two recent studies reported their findings on the prognosis of white matter hyperintensities separately on subgroups of patients with suspected cardioembolic index stroke[106] and patients with AF.[83] None of these studies found any association between white matter hyperintensities and the risk of ischemic stroke recurrence in these two subgroups, whereas they confirmed a higher risk of stroke recurrence in those subgroups of patients who had large-artery atherosclerosis and small-artery disease-related stroke[106] and those without AF.[83]

To sum up, the majority of the previous studies evaluating the association between white matter hyperintensities and ischemic stroke recurrence find an increased stroke risk in patients with severe white matter hyperintensities. However, a recent well-conducted study from Finland[96] in young stroke patients and an older study[100] found no association. Furthermore, the prognostic significance of white matter hyperintensities may differ with the time perspective and in cardioembolic versus non-cardioembolic ischemic stroke.

Mortality and Cardiovascular Events

In the general population, a number of studies have shown that white matter hyperintensities are associated with increased mortality.[45,92,94,107] In a meta-analysis of these studies, the hazard ratio of death was 2.3 (95% CI 1.9-2.8) for severe white matter hyperintensities.[108]

In ischemic stroke patients as well, white matter hyperintensities seem to be associated with an increased mortality. In recent studies, the hazard ratios of death in patients with moderate-to-severe white matter hyperintensities varied from 1.6 (95% CI 1.2-2.2) to 2.02 (95% CI 1.03-3.96).[103,104,109] In the study by Putaala et al.[96] in

young stroke patients, the adjusted hazard ratio of death from any cause was 3.42 (95% CI 1.58-7.42) in patients with moderate-to-severe white matter hyperintensities after a mean follow-up of 8.7 years. In the Danish Copenhagen Stroke Study, leukoaraiosis had no significant influence on mortality.[110] Debette et al.[108] included four studies on high-risk patients in a meta-analysis of white matter hyperintensities and mortality. These studies comprised patients with stroke, headache, dizziness, and imbalance. White matter hyperintensities were associated with an increased mortality with a hazard ratio of 1.6 (95% CI 1.01-2.7).

The association between white matter hyperintensities and the risk of cardiovascular events in stroke patients has only been reported in a limited number of studies. van Swieten et al.[98] investigated the risk of cardiac events in patients with white matter hyperintensities and found a hazard ratio of 1.4 (95% CI 0.9-2.1). Puttala et al.[96] found an insignificantly lower risk of cardiovascular events in patients with severe white matter hyperintensities with a hazard ratio of 0.82 (95% CI 0.38-1.76). In the LiLAC study cohort[68], the long-term (mean 10.1 years) risk of vascular events was increased in those with white matter hyperintensities on CT with a hazard ratio 1.42 (95% CI 1.22-1.66).

To conclude, white matter hyperintensities seem to be associated with an increased mortality in ischemic stroke patients. The association between white matter hyperintensities and cardiovascular events is uncertain.

4.2. IMPROVEMENT OF RISK PREDICTION MODELS

One of the aims of Study 2 was to investigate the potential of including white matter hyperintensities as a measure to improve the predictive ability of the CHA_2DS_2VASc score and the Essen Stroke Risk Score. A basic requirement for a new predictor is its independent association with the outcome of interest. Hence, this must be evaluated before incorporating the predictor into the model. D'Agostino stated that "the new variable must be statistically significant and its relative risk must be clinically meaningful".[111] He proposed that an at least two-fold increase in relative risk from the first to the last quartile is reasonable. Based on the existing literature as cited above, it seems fair to assume that this could be true for white matter hyperintensities and stroke recurrence.

Other factors to consider are the distribution or the prevalence of the predictor, the observer variability in the assessment of the predictor, and the weighting of the predictor.[47] A predictor present in only 1% of the population is of questionable value. We know from the literature that white matter hyperintensities are a common finding; hence, this is not of major concern. The observer variability is a relevant consideration in our case. White matter hyperintensities can be graded on various rating scales and the presence of inter-observer variability cannot be disputed.[43] We

chose to grade the radiological changes on the Fazekas scale which is relatively simple and among the most commonly applied rating scales.[112] However, the issue of inter-observer variability of the rating should be more thoroughly explored before clinical application. The CHA_2DS_2VASc score as well as the Essen Stroke Risk Score are point-based models. To keep the simplicity of the concept of point-based models, we decided to add one point to the scores for a given cutoff of the severity of the white matter hyperintensities.

A described in Chapter 3, the C-statistic is the most commonly applied statistical measure of model performance. In the evaluation of the performance of a new model, the C-statistic of the new and the old models can be compared. An increment in the C-statistic is equivalent to an improvement of the discriminatory performance of the model. However, it should be noted that models in which the original score has a relatively high C-statistic are relatively harder to improve in terms of a significantly higher C-statistic.[74] We calculated and compared the C-statistics as the primary measure of model performance.

The net reclassification improvement (NRI) has been proposed as a supplementary measure in the evaluation of new predictors.[113] The NRI measures the number of individuals among events and non-events changing category after the addition of a new predictor. Among the individuals with the event of interest, a net reclassification upwards in risk category indicates that the predictor is beneficial. The opposite is true for the individuals without the event, that is, a downward reclassification is also considered beneficial. The total NRI is calculated as the sum of movements for events and non-events.[74] The interpretation and the meaning of this measure has been disputed.[114] However, here I report the NRI as an additional analysis as the reclassification table may offer useful information.

Improving Stroke Risk Prediction with Neuroimaging

Two previous studies have evaluated whether existing stroke risk scores can be improved by adding imaging markers of cerebral small vessel disease. Poels et al. applied data from the Rotterdam Scan Study and added information on silent brain infarcts and white matter hyperintensities to the Framingham Stroke Risk Function.[93] Their study was based on MRI scans from a population-based cohort and assessed the risk of incident stroke (ischemic and hemorrhagic). They found an improved accuracy of the 10-year stroke prediction when adding silent brain infarcts and periventricular white matter hyperintensities to the original score. No improvement was found for the addition of subcortical white matter hyperintensities.

In a study from the Athens Stroke Registry[83], the authors evaluated the potential improvement in the discriminatory performance of stroke prediction of the $CHADS_2$ and the CHA_2DS_2VASc scores when adding one point for leukoaraiosis on CT or MRI. The cohort comprised patients with incident ischemic stroke. None of the risk

scores showed improved discrimination when augmented with information on leukoaraiosis. Hence, the concept of adding neuroimaging markers of cerebral small vessel disease to existing risk score schemes has proved feasible. Yet, until now it has been confirmed only in a population-based cohort and as an extension of the Framingham Stroke Risk Function.

4.3. STUDY 2

Results

Study 2 was a register-based cohort study on patients with incident ischemic stroke and no AF. Patients were identified in the Danish Stroke Registry. The study cohort was restricted to patients admitted to Aalborg University Hospital or Hjørring Hospital in the period from 1 January 2005 to 31 December 2012. Furthermore, only patients who underwent an MRI brain scan within 4 weeks after the index stroke were included.

Review and rating of the MRI scans were a central part of this study. White matter hyperintensities were rated according to the Fazekas scale.[112] Deep white matter hyperintensities (DWMH) and periventricular hyperintensities (PVH) were rated separately, and the total Fazekas score was calculated as the sum of the DWMH and the PVH (collectively referred to as the neuroimaging scores). We calculated recalibrated clinical scores by adding one point for white matter hyperintensities scores above various thresholds to the CHA_2DS_2VASc score and the Essen Stroke

Table 3. C-statistics for the clinical scores, the combination of the clinical scores and a DWMH score ≥ 2, and the neuroimaging scores.

	Recurrent ischemic stroke	Death	Cardiovascular events
CHA_2DS_2VASc score	0.59 (0.51-0.65)	0.70 (0.64-0.77)	0.59 (0.54-0.65)
Essen Stroke Risk Score	0.60 (0.53-0.68)	0.69 (0.62-0.76)	0.60 (0.55-0.65)
CHA_2DS_2VASc score + DWMH score ≥2	0.62 (0.54-0.70)	0.72 (0.66-0.78)	0.61 (0.56-0.67)
Essen Stroke Risk Score + DWMH score ≥2	0.63 (0.56-0.71)	0.71 (0.65-0.77)	0.62 (0.57-0.67)
DWMH score	0.65 (0.58-0.73)	0.65 (0.66-0.78)	0.59 (0.54-0.65)
PVH score	0.62 (0.52-0.68)	0.66 (0.61-0.72)	0.58 (0.53-0.63)
Total Fazekas score	0.65 (0.58-0.73)	0.67 (0.61-0.73)	0.60 (0.54-0.65)

The CHA_2DS_2VASc score and the Essen Stroke Risk Score were recalibrated by adding one point for a DWMH score ≥2. Abbreviations: DWMH = deep white matter hyperintensity; PVH = periventricular hyperintensity. Data are C-statistics (95% CI).

Risk Score. C-statistics were calculated for the clinical scores, the recalibrated clinical scores, and the neuroimaging scores.

The study comprised 832 patients with a mean age of 59.5 (standard deviation (SD) 13.9) years. In the adjusted analyses, we found white matter hyperintensities to be significantly associated with the risk of recurrent ischemic stroke. There was a trend towards a significant association between white matter hyperintensities and the risk of death and cardiovascular events. The C-statistics are shown in Table 3. For the outcome of recurrent ischemic stroke, we found a statistically significant improvement of the C-statistics of the clinical scores when recalibrated by adding one point for a DWMH score ≥2 and a total Fazekas score ≥4. The differences were not significant for the thresholds of DWMH =3 and a total Fazekas score =6. For the outcomes of death and cardiovascular events, the C-statistics of the recalibrated scores were not significantly higher than the original scores. The numerically highest C-statistics were observed for the DWMH score and the total Fazekas score. However, these values were not significantly higher than those of the original scores.

Table 4. Net reclassification improvement after 1 year of follow-up.

	Patients reclassified, n (%)		NRI (95% CI)	*p*-value
	With event	Without event		
Recurrent ischemic stroke				
CHA_2DS_2VASc + DWMH ≥2	17 (63.0)	281 (36.4)	0.52 (0.13-0.91)	0.009
Essen Stroke Risk Score + DWMH ≥2	16 (59,3)	247 (32.0)	0.54 (0.16-0.91)	0.005
Death				
CHA_2DS_2VASc + DWMH ≥2	15 (45.5)	351 (44.2)	0.02 (-0.32-0.36)	0.89
Essen Stroke Risk Score + DWMH ≥2	14 (42.4)	212 (26.7)	0.31 (-0.03-0.65)	0.07
Cardiovascular events				
CHA_2DS_2VASc + DWMH score ≥2	23 (40.3)	191 (25.8)	0.29 (0.02-0.56)	0.04
Essen Stroke Risk Score + DWMH ≥2	23 (40.3)	191 (25.8)	0.29 (0.02-0.57)	0.04

Abbreviations: NRI = Net reclassification improvement; DWMH = deep white matter hyperintensity score.

Net reclassification improvement after 1 year of follow-up is shown in Table 4. The recalibrated models showed improved classification for the outcomes of recurrent ischemic stroke and cardiovascular events when adding 1 point for a DWMH score ≥2.

Study-Specific Methodological Considerations on Study 2

As in Study 1, the study cohort in Study 2 was identified in the Danish Stroke Registry. We restricted the population to patients admitted to Aalborg University Hospital and Hjørring Hospital as these were the quantitatively largest stroke units in the North Denmark Region. We had access to imaging data only from examinations performed in this region.

An important issue in the preparation of Study 2 was the management of the imaging data. CT was available in the majority of the patients, whereas MRI was available only in a subgroup of patients. The sensitivity and reproducibility of MRI rating of white matter hyperintensities are greater than those of CT,[115,116] and most modern studies on this topic are based on MRI. Before the initiation of the studies, we assessed the number of MRI scans in the archives by counting the number of scans as there were no pre-existing imaging data in the patients. We found the number to be reasonable. We therefore chose to restrict the study population to patients with an available MRI brain scan. However, there were important demographic and clinical differences between the patients with and without an available MRI scan, which limits the generalizability of this study.

Attention was paid to the fact that white matter hyperintensities may be of non-small vessel disease origin. Differential diagnoses of white matter hyperintensities include acquired as well as hereditary diseases like multiple sclerosis and leukodystrophies.[117] Various patterns of distribution and localization of the white matter changes will raise suspicion of alternative underlying etiologies. The presence of other signs of small vessel disease (lacunes, microbleeds, enlarged perivascular spaces) supports the small vessel etiology.[118] Cases of uncertainty were conferred with a consultant neuroradiologist and resolved by consensus discussion.

In Study 1, more than one fourth of the patients died during follow-up and we therefore considered death a competing risk. In Study 2 and Study 3, about 9% of the study population died during follow-up. In these studies, we therefore chose to ignore the issue of competing risks.

Discussion

The findings obtained in Study 2 were in accordance with the findings from the majority of the studies listed in Table 2: White matter hyperintensities were associated with an increased risk of recurrent ischemic stroke, even after adjusting for vascular risk factors comprised in the CHA_2DS_2VASc score. Furthermore, this

study clearly demonstrated a dose-response relation between the burden of white matter hyperintensities and the risk of ischemic stroke recurrence. This was true for the deep as well as the periventricular white matter hyperintensities and for the total Fazekas score. Only one study listed in Table 2 assessed potential differences in the significance of deep versus periventricular hyperintensities. Kim et al.[105] found that extensive periventricular but not subcortical white matter hyperintensities were associated with the 90-day stroke recurrence risk. This is surprising as it has been suggested that periventricular hyperintensities are of non-vascular origin.[119] Our study did not support the indications of a substantially different prognostic value of periventricular versus deep white matter hyperintensities.

We chose to add one point to the clinical scores for a DWMH score ≥2. In our data, the DWMH score was more strongly associated with the ischemic stroke recurrence risk than the PVH score. It is easier to assess the DWMH score than the total Fazekas score, especially for the non-radiologist, as only the deep white matter is rated. This is important for the clinical utility of the DWMH score which is intended for stroke neurologists. However, as shown in the sensitivity analyses, the results applied for a total Fazekas score ≥4 as well.

The results of Study 2 are conceptually in accordance with those reported in the study by Poels et al.[93] extending the Framingham Stroke Risk Function. On the other hand, the results contrast with the findings from the Athens Stroke Registry.[83] In the interpretation of these apparently conflicting results, there are some essential methodological differences to consider. We, and Poels et al., applied exclusively MRI in the rating of the white matter hyperintensities. As a result, we were able to make a detailed rating and to differentiate between deep and periventricular changes. In the study based on the Athens Stroke Registry, both CT and MRI were allowed, and leukoaraiosis was reported only as present or not present. Though the applied rating scale is validated for the application in both CT and MRI,[116] this may have hampered the study. Also, as we have shown, adding a point for moderate white matter hyperintensities (DWMH ≥2 or total Fazekas score ≥4) but not for the most severe changes (DWMH =3 or total Fazekas score =6) improved the discriminatory power. The rating of leukoaraiosis in the Greek study was not described in details; thus, it cannot be ruled out that "leukoaraiosis" in their terms represented only the most severe changes.

Interestingly, the scores based solely on neuroimaging showed the best discriminatory performance in stroke recurrence prediction. The DWMH score and the total Fazekas score had C-statistics of 0.65, which were even better than the recalibrated clinical scores. The C-statistics of the neuroimaging scores were not statistically significantly higher than those of the clinical scores, although the recalibrated scores were significantly better. This paradox was caused by the close correlation between the clinical and the recalibrated clinical scores resulting in more narrow confidence intervals on the difference between these two scores.

Notwithstanding these statistical details, the neuroimaging scores proved useful in stroke recurrence prediction in our cohort.

Several unanswered questions regarding white matter hyperintensities and ischemic stroke remain. Future studies should address the potentially different prognostic values of white matter hyperintensities in AF versus non-AF patients, the short-term prognosis versus the (very) long-term prognosis, and the deep versus the periventricular changes. We have proved the potential for improving clinical stroke risk scores by adding moderate-to-severe white matter hyperintensities as a predictive variable. However, the results should be confirmed in larger cohorts with more events and longer follow-up that will permit risk assessment in clinically relevant periods such as 1, 5, and 10 years. Moreover, future research should clarify whether risk scores based on white matter hyperintensities are superior to clinically based risk scores in stroke patients in general. An area of interest is whether there is a potential for enhancing the neuroimaging scores, for instance by combining various signs of small vessel disease or by adding selected clinical variables.

Conclusions on Study 2

In conclusion, white matter hyperintensities were associated with an increased risk of recurrent ischemic stroke in non-AF stroke patients. Second, the recalibration of the CHA_2DS_2VASc score and the Essen Stroke Risk Score with information on white matter hyperintensities resulted in improved discriminatory performance and improved classification. Third, the scores based solely on neuroimaging had the numerically highest C-statistics.

CHAPTER 5. SILENT LACUNES AND RECURRENT ISCHEMIC STROKE

Lacunes are "black holes" in the brain – small fluid-filled cavities with imaging signal characteristics similar to those of the cerebrospinal fluid. Like white matter hyperintensities, lacunes are considered a sign of cerebral small vessel disease.[33,38] A lacune may have been symptomatic or clinically silent. The clinical event corresponding to the symptomatic lacune is the lacunar stroke, resulting from a small brain infarct. Silent lacunes have no history of corresponding clinical symptoms. It remains unknown why some lacunes cause clinical symptoms, whereas others do not.[120] Similarly, for unknown reasons, not all lacunar infarcts will cavitate and develop a lacune.[121]

In Study 3, we aimed to investigate the association between silent lacunes and the risk of recurrent ischemic stroke, death, and cardiovascular events. Furthermore, we investigated the potential for enhancing clinical risk scores with silent lacunes. In this chapter, I will review the literature on the prognosis of silent lacunes and then present and discuss the results.

5.1. SILENT LACUNES AND PROGNOSIS

Ischemic Stroke

Most of the current knowledge on the prognostic significance of silent lacunes comes from studies that investigated the prognosis of the broader concept of silent brain infarcts. No universally accepted definition of silent brain infarcts exists. However, usually all types of infarcts are included: lacunar infarcts, cortical infarcts as well as territorial infarcts. In the Rotterdam Scan Study, lacunes constituted 95% of the silent brain infarcts.[40] Hence, it seems reasonable to assume that data from studies on silent brain infarcts largely apply in the prognosis of silent lacunes.

The prevalence and prognostic role of silent brain infarcts have been investigated in large population-based cohorts. The prevalence of silent brain infarcts varies with age, from about 5-10% in those aged 60 years to 25-35% in those above 80 years.[35] In the Framingham Offspring Study[45] and in the Rotterdam Scan Study,[90] the presence of silent brain infarcts increased the risk of stroke about 3-fold. Of note, these studies did not differentiate between ischemic and hemorrhagic strokes.

Table 5 summarizes studies on the prognosis of silent brain infarcts in ischemic stroke patients. The number of studies is limited compared with the literature on white matter hyperintensities. Two studies on the risk of stroke recurrence[96,122] found an

increased risk of stroke recurrence after mean follow-up of 2 years and 8 years, respectively. In the study by Putaala et al.,[96] this applied only for the presence on multiple (≥2) silent infarcts. In the study by de Jong et al.,[122] the risk of stroke

Table 5. Studies on silent brain infarcts and the risk of recurrent stroke and mortality.

Study	N; age; imaging modality	Main findings
Boon (1994)[125]	N=755; mean age 71 (range 24-96) years; CT	Patients with first-ever supratentorial stroke. After 30 days, and 1 year of follow-up, ORs for death were 0.97 (0.51-1.87) and 1.11 (0.73-1.70), respectively. No specific data on recurrent stroke.
Jørgensen (1994)[126]	N=500; mean age 74.3 (SD 11.5) years; CT	Patients with first-ever stroke (7.8% were hemorrhagic). Mortality rate during hospital stay did not differ. No specific data on stroke recurrence.
Brainin (1995)[127]	N=728; mean age 68 (SD 10) years; CT	Patients with first-ever ischemic stroke. After 3 years of follow-up, there were no differences in mortality. No specific data on stroke recurrence.
EAFT Study Group (1996)[123]	N=985; mean age not stated; CT	Patients with TIA or minor ischemic stroke and AF. Comparisons of patients with silent versus symptomatic lesions (a total of 532 patients) showed HR for recurrent stroke 1.18 (95% CI 0.79-1.77), HR for vascular events 1.2 (95% CI 0.9-1.6).
de Jong (2002)[122]	N=333; mean age not stated; CT	Patients with lacunar stroke. After a mean follow-up of 785 (SD 479) days the OR for recurrent stroke was 2.09 (95% CI 1.08-4.06) and the OR for mortality was 1.74 (95% CI 1.01-3.01). The results were not significant at 30 days and 1 year of follow-up.
Putaala (2011)[96]	N=655; mean age 40.0 years; MRI	Patients with first-ever ischemic stroke. After a mean follow-up of 8.3 (SD 4.0) years, HRs for recurrent stroke were 1.47 (0.68-3.16) for a single SBI and 2.48 (1.24-4.94) for multiple SBIs. Estimates for cardiovascular events and death were around 1.3, but not significant.
Goia (2012)[151]	N=170; mean age 39.4 (SD 8.5) years; MRI	Patients with first-ever ischemic stroke. After a mean follow-up of 26 (SD 23.0) months, silent ischemic lesions (leukoaraiosis *or* SBI) were associated with an HR of 3.2 (95% CI 1.2-8.7) for recurrent stroke; the HR for recurrent stroke with the combination of SBI *and* leukoaraiosis was 7.3 (2.3-22.9). No data on isolated SBI.
Weber (2012)[124]	N=207/207; mean age 66.1 (SD 8.5) years; MRI	Case-control study of patients with recent non-cardioembolic stroke. After a mean follow-up of 2.5 years, OR for recurrent stroke was 1.42 (95% CI 0.79-2.46), OR for cardiovascular events was 1.38 (95% CI 0.81-2.33), and OR for death was 2.33 (95% CI 0.90-6.07).

Abbreviations: CT, computed tomography; OR, odds ratio; SD, standard deviation; CI, confidence interval; HR, hazard ratio; MRI, magnetic resonance imaging; AF, atrial fibrillation; SBI, silent brain infarct.

recurrence was increased after 2 years of follow-up, whereas the risk was not significantly increased after 30 days or 1 year of follow-up. Two other studies on patients with AF[123] and patients with non-cardioembolic stroke[124] found no increased risk of stroke recurrence in the group with silent brain infarcts.

Mortality and Cardiovascular Events

Three older studies[125–127] investigated the mortality in ischemic stroke patients during the hospital stay and during up to 3 years of follow-up. None of these studies found any differences between patients with or without silent brain infarcts. Nor did the two newer studies by Putaala et al.[96] and Weber et al.[124] find an increased mortality. Only in the study by de Jong et al.[122] were silent infarcts associated with a statistically significantly increased risk of death at the end of follow-up. None of the studies found an increased risk of vascular events.

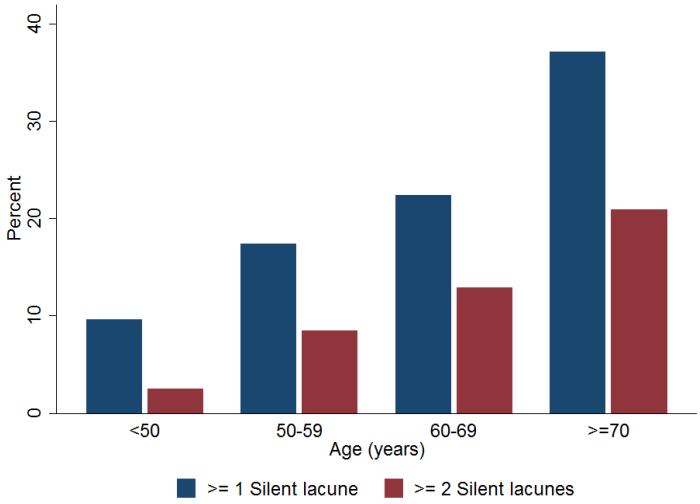
To sum up, the existing literature indicates a possibly increased risk of stroke recurrence in ischemic stroke patients with silent brain infarcts. Most of the evidence indicates no increased risk of death in ischemic stroke patients with silent brain infarcts; nor does the risk of vascular events seem to be increased.

5.2. STUDY 3

Results

The study cohort of Study 3 was identical to the study cohort of Study 2 with the exception that patients with a previous TIA were excluded. This produced a cohort of 786 patients with a mean age of 59.5 (SD 14.0) years. Analyses were stratified on the number of lacunes, classified as none, a single or multiple silent lacunes. As seen from Figure 1, the prevalence of silent lacunes was strongly dependent on age. Besides age, the presence of at least one silent lacune was more common in patients with congestive heart failure, hypertension, impaired renal function, in females, and in patients with moderate-to-severe white mater hyperintensities. The cumulative risk and the incidence rates of recurrent ischemic stroke and cardiovascular events increased with the number of silent lacunes. For the outcome of death, the correlation was more ambiguous. In the Cox proportional hazard analyses, the presence of multiple silent lacunes was associated with an increased risk of ischemic stroke recurrence. This finding persisted after adjustment for age, sex, and vascular risk factors. In the model additionally adjusted for white matter hyperintensities, the trend persisted, but it was statistically insignificant. We found no significant association between silent lacunes and the risk of death or cardiovascular events.

Figure 1. Age-specific prevalence of ≥1 and ≥2 silent lacunes.



In additional analyses, the discriminatory performance of the CHA_2DS_2VASc score and the Essen Stroke Risk Score was investigated when recalibrated with one point for the presence of multiple silent lacunes. In the prediction of recurrent ischemic stroke, the improvements in terms of the C-statistic were minor and not statistically significant. The CHA_2DS_2VASc score versus the recalibrated CHA_2DS_2VASc score resulted in C-statistics of 0.58 (95% CI 0.51-0.67) and 0.60 (95% CI 0.52-0.69), respectively (p=0.098); the Essen Stroke Risk Score versus the recalibrated Essen Stroke Risk Score resulted in C-statistics of 0.61 (95% CI 0.53-0.69) and 0.62 (95% CI 0.55-0.70), respectively (p=0.187).

Study-Specific Methodological Considerations on Study 3

The considerations related to study cohort selection and generalizability described in the previous chapter on Study 2 apply in Study 3 as well. Besides these considerations, a number of other important potential weaknesses should also be considered. The correctness of "clinical silence" of the observed lacunes was based on the registry information. We excluded patients registered with a previous TIA. However, we still cannot guarantee that some patients with lacunes could have been assessed as symptomatic if the patient had been interviewed and examined clinically. Some TIAs or minor strokes may have caused subtle or odd symptoms that the patient, or even the doctor, did not react upon. If present, these events would represent potential cases of misclassification.

Table 6. Cox proportional hazard analysis showing crude and adjusted hazard ratios of recurrent ischemic stroke.

	Recurrent ischemic stroke		
Number of silent lacunes	Crude HR (95% CI)	Model 1 Adjusted HR (95% CI)[a]	Model 2 Adjusted HR (95% CI)[b]
0	Reference	Reference	Reference
1	1.60 (0.71-3.62)	1.53 (0.67-3.49)	1.35 (0.58-3.11)
≥2	3.05 (1.61-5.81)	2.52 (1.25-5.09)	1.62 (0.74-3.55)

[a]) Model 1: Hazard ratios were adjusted for age, sex, congestive heart failure, hypertension, diabetes, and vascular disease. [b]) Model 2: Adjusted for the factors in model 1 and white matter hyperintensities.

Another important consideration is the correct identification of lacunes. Of special concern is the confusion of lacunes and enlarged perivascular spaces, also known as Virchow-Robin spaces.[38] Like lacunes, enlarged perivascular spaces show MRI signal characteristics similar to those of the cerebrospinal fluid and they are often located in the basal ganglia. These two entities are mainly distinguished by their size: perivascular spaces are smaller than 3 mm in diameter, whereas lacunes are larger than 3 mm. Lacunes are usually surrounded by a T2 hyperintense ring, which lacks in perivascular spaces.[38,128] Moreover, enlarged perivascular spaces are usually multiple and symmetrically distributed. These features were carefully considered in the rating; however, some cases of misclassification cannot be precluded. It should also be noticed that the smallest lacunes could be missed due to the slice gap on the MRI, which is usually 5 mm.

Discussion

In terms of absolute risks, we demonstrated a moderate difference between patients with no versus multiple silent lacunes: After 3 years of follow-up, the risk of stroke recurrence was 5% versus 11%, respectively. In the multivariable model adjusted for age, sex, congestive heart failure, hypertension, diabetes, and vascular disease (model 1 in Table 6), we found that multiple silent lacunes were associated with a 2.5 times higher risk of ischemic stroke recurrence.

In comparison, a total Fazekas score of 6 was associated with a more than five times higher risk of stroke recurrence. Hence, white matter hyperintensities seem to be more closely associated with the risk of recurrent ischemic stroke than silent lacunes. Of note, the number of patients with multiple silent lacunes and the most severe

grades of white matter hyperintensities (total Fazekas score 5-6) were almost the same in Study 3 – 11.1% versus 13.5%, respectively. As previously described, lacunes and white matter hyperintensities are both considered to be signs of cerebral small vessel disease, and the reasons for these considerable differences in the association with stroke recurrence are not obvious.

One possible explanation is that lacunes form a more heterogeneous entity than white matter hyperintensities. We based the definition of lacunes on current recommendations,[38] and the size is an important characteristic in this definition. The size limits may to some extent be arbitrary, and not all "true" lacunes may fall within these limits.[33] Furthermore, it is not certain that silent lacunes constitute an independent entity.[32] Others have argued that two types of lacunar infarction exist: one type related to small vessel disease and another type related to large-vessel atherosclerotic disease and embolism; and that these may differ in location.[33,122] Lacunes in the basal ganglia are presumably more likely to be caused by large-artery or cardiac embolism. Opposite, lacunes in the centrum semiovale most likely result from occlusion of small perforators.[33] Hence, some silent lacunes may be of non-small vessel disease origin which could blur the effect of "true" small vessel disease-related silent lacunes. Of course, this implies that these two different entities carry different prognoses. Another observation of unknown significance is that some lacunes develop from lacunar infarcts, whereas others develop in areas of intense white matter hyperintensities without evidence of previous infarction.[33] Hence, there are several unknown factors regarding the pathogenesis of lacunes.

White matter hyperintensities were associated with an increased risk of death and cardiovascular events, whereas silent lacunes were not. This further indicates important differences in the prognostic significance of white matter hyperintensities and silent lacunes and supports that there may be different underlying pathogeneses,[129] though these are so far largely unknown.

In the additional model (model 2 in Table 6), we further adjusted for white matter hyperintensities. This considerably weakened the association between multiple silent lacunes and recurrent ischemic stroke, which was a consequence of the close association between silent lacunes and white matter hyperintensities as shown by a Goodman and Kruskal's gamma of 0.695. The consequence of this is that for the purpose of risk prediction, silent lacunes will add no further value to a model already including white matter hyperintensities. Importantly, this does not necessarily imply that the presence of silent lacunes holds no prognostic information. As stated above, the presence of multiple silent lacunes more than doubles the risk of a second stroke during the first 3 years. However, in our analyses, silent lacunes showed no potential for significantly enhancing the discriminatory performance of the CHA_2DS_2VASc score or the Essen Stroke Risk Score. Poels et al. found very similar results in their population-based study.[93] They added information on silent brain infarcts to the Framingham Stroke Risk Function and found only minor improvements in the C-

statistic (0.01-0.04) with the greatest improvement in women. They did not report whether the improvements were statistically significant.

Conclusions on Study 3

Multiple silent lacunes were significantly associated with an increased risk of recurrent ischemic stroke in non-AF patients, but silent lacunes showed no potential for enhancing the discriminatory performance of the CHA_2DS_2VASc score or the Essen Stroke Risk Score in stroke risk prediction. There were no significant associations between silent lacunes and the outcomes of death and cardiovascular events.

CHAPTER 6. GENERAL METHODOLOGICAL CONSIDERATIONS

All studies are subject to error. Different types of studies are prone to different types of error. Overall, errors can be either systematic or random. The former include bias and confounding, and precautionary measures can be taken to prevent these errors. Random errors are inevitable, but their significance can be reduced by increasing the size of the sample or study cohort.[78]

Selection Bias

Selection bias arises when the associations between the exposure and the outcome differs between those included in the study and those not included.[78,130] In Study 1, we included all patients (except those with AF) registered in the Danish Stroke Registry with a diagnosis of incident ischemic stroke in the period 2003-2012. The completeness and the validity of this registry is high,[9,82] and there are no indications that the included patients were not representative of Danish stroke patients.

In Study 2 and Study 3, we also identified patients in the Danish Stroke Registry. Eligible patients were restricted to those admitted to Aalborg University Hospital and Hjørring Hospital in the period 2005-2012. This geographical restriction may have introduced a minor selection bias as differences between patients in different regions of the country may exist, such as disparities in lifestyle, comorbidities, and the willingness to seek medical care. However, a more severe selection bias was introduced by including only patients who underwent an MRI scan. As documented, these patients were younger, had less severe strokes, and a lower burden of comorbidities than those not included. Therefore, caution should be taken when generalizing the results to other populations.

Information Bias

Information bias refers to incorrect measuring or classification of information on the variables in the study. Incorrect classification, or misclassification, can be differential or non-differential.[78,130] Either type of misclassification affects the estimates differently. In differential misclassification, the erroneous classification is related to other variables, and the effect on the estimates is unpredictable. Non-differential misclassification is misclassification unrelated to other variables and tends to draw the effect estimates towards neutrality.[130]

In Study 1, the exposures were the CHA_2DS_2VASc score and the Essen Stroke Risk Score. We applied previously validated algorithms for the calculation of the scores,[49] and we combined this information with data on comorbidities from the Danish Stroke Registry to increase sensitivity. Thus, in our algorithms, we were not able to identify patients with hypertension and diabetes treated with non-pharmacological methods. Individual assessment of the CHA_2DS_2VASc score and the Essen Stroke Risk Score by a physician may have resulted in different scores, and misclassification therefore cannot be ruled out. Any existing misclassification is, however, considered to be non-differential.

In Study 2 and Study 3, the exposures were the burden of white matter hyperintensities and the number of silent lacunes, respectively. The rating of the images was performed by the PhD student who had had training sessions with a consultant neuroradiologist. A reference panel of pre-rated images was regularly reviewed.[131] The consultant neuroradiologist rated a validation sample, and we found acceptable agreement between the two raters. In no patients did we find disagreements of more than one point on the Fazekas scale. The rating of the images was performed blinded to all outcomes and variables; still, blinding of the civil registration number was not possible as knowledge of this this number was necessary to access the images. Thus, this could be a potential source of differentiated misclassification.

The outcomes in all three studies were recurrent ischemic stroke, death, and cardiovascular events, though emphasis was on recurrent ischemic stroke. Diagnoses of recurrent stroke were identified in the Danish Stroke Registry, whereas all other diagnoses were identified in the Danish National Patient Registry. Recently, the Danish Stroke Registry was validated and the positive predictive value of a stroke diagnosis was found to be 90%.[82] Information on death was obtained from the Danish Civil Registration System. No validation studies exist on this registry. However, in general the quality and coverage is assumed to be very high and no significant misclassification is suspected.[132] Cardiovascular events were defined as the composite endpoint of ischemic stroke, TIA, myocardial infarction, and arterial thromboembolism. The positive predictive value of the TIA diagnosis in the Danish National Patient Registry is 58-68%.[133,134] The negative predictive value is unknown. The positive predictive value of myocardial infarction is above 80%,[135] whereas the validity of arterial thromboembolism is unknown. The validity of the TIA diagnosis is problematic. TIA constituted 29-40% of the events in the outcome of cardiovascular events, and the number of cardiovascular events may have been overestimated. This potential misclassification is suspected to be non-differential, hence drawing the estimates towards the null.

Confounding

In epidemiology, confounding refers to the confusion of effects.[78,136] A confounder must be associated with the exposure as well as the outcome. The confounder may not be an effect of the exposure, and it must be causally related to the outcome, or be a proxy for a cause of the outcome.[78] Confounding is a systematic error and should be prevented by careful planning of the study and through the analyses; however, complete elimination of confounding is illusory.

In all three studies, we restricted the study population to patients with incident ischemic stroke. This ensured a more homogenous study population and elimination of potential confounding from previous strokes. It is not the number of previous strokes *per se* that might confound the effects of the exposure, but this number could be a proxy for factors associated with the outcomes.

In Study 1, we investigated the performance of two existing risk prediction models; and we did not aim to assess the direct effects of the exposure variables on the outcomes. Therefore, no further confounder control was included in the analyses.

In Study 2 and Study 3, we investigated the effect of white matter hyperintensities and silent lacunes on the risk of the outcomes. We assumed that the risk factors included in the CHA_2DS_2VASc score were associated with the exposure (white matter hyperintensities and silent lacunes) and with the outcomes; furthermore, we did not consider the individual factors in the CHA_2DS_2VASc score to be intermediates between the exposure and the outcome. We accordingly adjusted for these potential confounders in the multivariable Cox proportional hazards models. In Study 3, we also included white matter hyperintensities in an additional model as previously discussed.

Missing Data

As described above, the CHA_2DS_2VASc score and the Essen Stroke Risk Score were calculated by combining information from The Danish Stroke Registry with data from the National Prescription Registry and the Danish National Patient Registry. In the two latter registries, there are no missing data as such – this is only a question of validity of the recorded diagnose. In The Danish Stroke Registry, the frequencies of missing data of the applied variables were as follows: diabetes 3.7%; previous myocardial infarction 4.6%; hypertension 4.9%; previous TIA 5.5%; peripheral arterial disease 8.6%; and smoking status 12.1%. Any data missing in the Danish Stroke Registry were coded as "not present". No specific measures were taken to address missing data further.

Random Error

In the previous paragraphs, I have discussed potential sources of systematic errors and how attempts were made to prevent them. Random errors are unexplained variability in the data.[78,130] Generally, the significance of random errors will diminish with increasing size of the study population. This is reflected in the size of the confidence intervals of the estimate. Small samples much influenced by random errors have broad confidence intervals, whereas large samples with little influence from random errors have narrow confidence intervals.[78] In the studies of this dissertation, efforts were made to maximize the size of the study cohorts and thereby to reduce random error. In Study 1, random error was a negligible problem.

Outcome Misclassification

The primary outcomes in all three studies were recurrent ischemic stroke, death, and cardiovascular events. It is possible that some cases of death were caused by undiagnosed stroke which would lead to misclassification. Regarding death, we assessed only all-cause mortality, though it would have been of interest to explore whether the clinical scores or the neuroimaging scores performed better in the prediction of stroke-related and/or cardiovascular death. To answer these questions, we would have needed access to reliable information on the causes of death. Information on the cause of death is available in the Danish Register of Causes of Death, which covers the entire Danish population since 1875 with diagnoses from the death certificates. However, it is open to doubt whether this could have answered the question satisfactorily as the validity of this register is debated.[137] Therefore, we did not pursue this further.

In all three studies, information on stroke subtype of the incident as well as the recurrent strokes would have strengthened the studies. A stroke subtype classification would have required review of the medical files and access to laboratory data and neuroimaging data from the recurrent strokes on all patients. The design of the studies and the anonymized processing of data did not allow for this.

CHAPTER 7. CONCLUSIONS AND PERSPECTIVES

The studies of this dissertation have contributed to clarify the value of contemporary clinical risk score schemes and neuroimaging signs of cerebral small vessel disease in the prediction of recurrent ischemic stroke, death, and cardiovascular events in non-AF patients with incident ischemic stroke. Validated risk stratification models are valuable clinical tools and may aid patient counseling and guide treatment decisions.

We used the CHA_2DS_2VASc score as a starting point for the studies. This score system is used widely in the clinic for stroke and thromboembolic risk stratification in AF patients and, moreover, the score has been validated in a number of other patient categories. Despite the promising potential of the CHA_2DS_2VASc score in various groups of patients, it was of limited value in stroke recurrence prediction in our cohort of non-AF ischemic stroke patients. The baseline risk of stroke recurrence was relatively high for those patients with the lowest score, and the presence of additional risk factors increased the recurrence risk only moderately. This was also true for the Essen Stroke Risk Score. The included risk factors did, however, show an additive effect on the absolute and the relative risks, but the added risk for each factor was very moderate. This is underscored by comparison with for instance the Framingham stroke risk score.[138] Therefore, the clinical utility of the CHA_2DS_2VASc score and the Essen Stroke Risk Score for the purpose of ischemic stroke recurrence prediction in non-AF patients is questionable, and based on the low discriminatory performance we cannot recommend routine clinical application of these scores for risk stratification purposes.

We were not able to differentiate patients based on the underlying cause of the stroke. Our cohort comprised patients with various etiologies of ischemic stroke; large-artery disease, small vessel disease, rare causes, and unknown etiologies. We therefore cannot exclude that the scores could perform better in distinct subgroups of patients. This issue could be a potential topic for future studies; however, pursuit of this idea would detract from our original objective which was do develop a risk score that could easily be applied in all (non-AF) stroke patients without the need for advanced investigations. From a clinical perspective, it can be argued that for a large number of the ischemic stroke patients, the etiology is relatively easily determined; hence, a subdivision according to the underlying cause could be meaningful.

The scores based on white matter hyperintensities showed the strongest association with the risk of stroke recurrence and the best discriminatory performance. The neuroimaging variables can be considered more specific in the sense that they are

directly related to the organ in question. Of course, this does not necessarily imply that they are better predictors of stroke recurrence risk; but the results presented in this dissertation confirm that in non-AF patients this is actually the case. The strong association between white matter hyperintensities and ischemic stroke recurrence resulted in a significantly better discriminatory performance of the clinical scores when recalibrated with one point for moderate-to-severe white matter hyperintensities. This important finding confirms the potential for enhancing existing scores with carefully selected new variables. Based on the results of Study 2, it may be speculated that recalibrating the Fazekas score or other neuroimaging scores with selected clinical variables could be a more advantageous approach resulting in even better discrimination. The size of our cohort did not allow for answering this question, but future studies with adequately sized cohorts are needed to explore this hypothesis.

The prognostic value of silent lacunes was weaker than expected from the study on white matter hyperintensities. Though lacunes and white matter hyperintensities are both considered signs of cerebral small vessel disease, we conclude that in relation to ischemic stroke recurrence, the specificity of white matter hyperintensities is superior to that of silent lacunes. One reason for this may be that lacunes are a more heterogeneous entity than white matter hyperintensities. Recent studies have focused on the total burden of small vessel disease[139,140] – that means including all the radiological signs connected to small vessel disease in a single rating: white matter hyperintensities, lacunes, enlarged perivascular spaces, and microbleeds. Perhaps such combined scales of all or a number of the variables will show even greater potential in stroke recurrence prediction than the focus on the individual signs presented here. Hopefully, future studies will show.

At present, we cannot recommend any changes in clinical practice based on the results presented in this dissertation. However, in particular the presence of severe white matter hyperintensities in a patient with ischemic stroke should warrant careful evaluation of possible secondary preventive initiatives because these patients have an almost five times higher risk of stroke recurrence within the next three years compared to patients with no white matter changes.

REFERENCES

1. Lip GYH, Nieuwlaat R, Pisters R, Lane D a, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. 2010;137(2):263-272.

2. Aho K, Harmsen P, Hatano S, Marquardsen J, Smirnov VE, Strasser T. Cerebrovascular disease in the community: results of a WHO collaborative study. *Bull World Health Organ*. 1980;58(1):113-130.

3. Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: A statement for healthcare professionals from the American heart association/American stroke association. *Stroke*. 2013;44(7):2064-2089.

4. A classification and outline of cerebrovascular diseases. II. *Stroke*. 1975;6(5):564-616.

5. Dansk Selskab for Apopleksi. *Referenceprogram for Behandling Af Patienter Med Apopleksi*. København 2012; 2013.

6. Strong K, Mathers C, Bonita R. Preventing stroke: saving lives around the world. *Lancet Neurol*. 2007;6(2):182-187.

7. Feigin VL, Lawes CMM, Bennett D a, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. *Lancet Neurol*. 2009;8(4):355-369.

8. Demant MN, Andersson C, Ahlehoff O, et al. Temporal trends in stroke admissions in Denmark 1997-2009. *BMC Neurol*. 2013;13(1):156.

9. Dansk Apopleksiregister. *Dansk Apopleksiregister Årsrapport 2014*.; 2014.

10. Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Hennerici MG. Classification of stroke subtypes. *Cerebrovasc Dis*. 2009;27(5):493-501.

11. Adams HP, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke*. 1993;24(1):35-41.

12. Kolominsky-Rabas PL, Weber M, Gefeller O, Neundoerfer B, Heuschmann PU. Epidemiology of ischemic stroke subtypes according to TOAST criteria: incidence, recurrence, and long-term survival in ischemic stroke subtypes: a population-based study. *Stroke*. 2001;32(12):2735-2740.

13. Bejot Y, Caillier M, Ben Salem D, et al. Ischaemic stroke subtypes and associated risk factors: a French population based study. *J Neurol Neurosurg Psychiatry*. 2008;79(12):1344-1348.

14. Alzamora MT, Sorribes M, Heras A, et al. Ischemic stroke incidence in Santa Coloma de Gramenet (ISISCOG), Spain. A community-based study. *BMC Neurol*. 2008;8:5.

15. Ihle-hansen H, Thommessen B, Wyller TB, Engedal K, Fure B. Risk factors for and incidence of subtypes of ischemic stroke. *Funct Neurol*. 2012;27(1):35-40.

16. Bogousslavsky J, Cachin C, Regli F, Despland PA, Van Melle G, Kappenberger L. Cardiac sources of embolism and cerebral infarction--clinical consequences and vascular concomitants: the Lausanne Stroke Registry. *Neurology*. 1991;41(6):855-859.

17. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *N Engl J Med*. 1995;333(24):1581-1587.

18. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008;359(13):1317-1329.

19. Berkhemer OA, Fransen PSS, Beumer D, et al. A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke. *N Engl J Med*. 2014;372(1):141217070022009.

20. Goyal M, Demchuk AM, Menon BK, et al. Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke. *N Engl J Med*. February 2015:150211090353006.

21. Saver JL, Goyal M, Bonafe A, et al. Stent-Retriever Thrombectomy after Intravenous t-PA vs. t-PA Alone in Stroke. *N Engl J Med*. 2015;372(24):2285-2295.

22. Boysen G, Truelsen T. Prevention of recurrent stroke. *Neurol Sci*. 2000;21(2):67-72.

23. EAFT Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) Study Group. *Lancet (London, England)*. 1993;342(8882):1255-1262.

24. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(12):1139-1151.

25. Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. *N Engl J Med*. 2011;364(9):806-817.

26. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365(10):883-891.

27. Camm a J, Lip GYH, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010

ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J*. 2012;33(21):2719-2747.

28. Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. *Europace*. August 2015:euv309.

29. Suzuki N, Sato M, Houkin K, et al. One-year atherothrombotic vascular events rates in outpatients with recent non-cardioembolic ischemic stroke: the EVEREST (Effective Vascular Event REduction after STroke) registry. *J Stroke Cerebrovasc Dis*. 2012;21(4):245-253.

30. Sumi S, Origasa H, Houkin K, et al. A modified Essen stroke risk score for predicting recurrent cardiovascular events: development and validation. *Int J Stroke*. 2013;8(4):251-257.

31. Furie KL, Kasner SE, Adams RJ, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the american heart association/american stroke association. *Stroke*. 2011;42(1):227-276.

32. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol*. 2010;9(7):689-701.

33. Wardlaw JM, Smith C, Dichgans M. Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging. *Lancet Neurol*. 2013;12(5):483-497.

34. Rost NS, Rahman RM, Biffi a, et al. White matter hyperintensity volume is increased in small vessel stroke subtypes. *Neurology*. 2010;75(19):1670-1677.

35. Vermeer SE, Longstreth WT, Koudstaal PJ. Silent brain infarcts: a systematic review. *Lancet Neurol*. 2007;6(7):611-619.

36. Cordonnier C, Al-Shahi Salman R, Wardlaw J. Spontaneous brain microbleeds: systematic review, subgroup analyses and standards for study design and reporting. *Brain*. 2007;130(Pt 8):1988-2003.

37. Doubal FN, MacLullich a. MJ, Ferguson KJ, Dennis MS, Wardlaw JM. Enlarged Perivascular Spaces on MRI Are a Feature of Cerebral Small Vessel Disease. *Stroke*. 2010;41(3):450-454.

38. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol*. 2013;12(8):822-838.

39. Breteler MMB, van Swieten JC, Bots ML, et al. Cerebral white matter

lesions, vascular risk factors, and cognitive function in a population-based study: The Rotterdam Study. *Neurology*. 1994;44(July):1246-1246.

40. Vermeer SE, Den Heijer T, Koudstaal PJ, Oudkerk M, Hofman A, Breteler MMB. Incidence and risk factors of silent brain infarcts in the population-based Rotterdam Scan Study. *Stroke*. 2003;34(2):392-396.

41. Vernooij MW, van der Lugt A, Ikram MA, et al. Prevalence and risk factors of cerebral microbleeds: The Rotterdam Scan Study. *Neurology*. 2008;70(14):1208-1214.

42. Kapeller P, Schmidt R, Enzinger C, Ropele S, Fazekas F. CT and MRI rating of white matter changes. *J Neural Transm Suppl*. 2002;(62):41-45.

43. Kapeller P, Barber R, Vermeulen RJ, et al. Visual rating of age-related white matter changes on magnetic resonance imaging: scale comparison, interrater agreement, and correlations with quantitative measurements. *Stroke*. 2003;34(2):441-445.

44. van Straaten ECW, Fazekas F, Rostrup E, et al. Impact of white matter hyperintensities scoring method on correlations with clinical data: the LADIS study. *Stroke*. 2006;37(3):836-840.

45. Debette S, Beiser A, DeCarli C, et al. Association of MRI markers of vascular brain injury with incident stroke, mild cognitive impairment, dementia, and mortality: the Framingham Offspring Study. *Stroke*. 2010;41(4):600-606.

46. Moons KGM, Royston P, Vergouwe Y, Grobbee DE, Altman DG. Prognosis and prognostic research: what, why, and how? *BMJ*. 2009;338:b375.

47. Steyerberg EW. *Clinical Prediction Models*. New York: Springer; 2009.

48. Gage BF, Waterman a D, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285(22):2864-2870.

49. Olesen JB, Lip GYH, Hansen ML, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *Bmj*. 2011;342(jan31 1):d124-d124.

50. Friberg L, Rosenqvist M, Lip GYH. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. *Eur Heart J*. 2012;33(12):1500-1510.

51. Ntaios G, Lip GYH, Makaritsis K, et al. $CHADS_2$, $CHA_2S_2DS_2$-VASc, and long-term stroke outcome in patients without atrial fibrillation. *Neurology*. 2013;80(11):1009-1017.

52. Mitchell LB, Southern D a, Galbraith D, Ghali W a, Knudtson M, Wilton SB.

Prediction of stroke or TIA in patients without atrial fibrillation using CHADS2 and CHA2DS2-VASc scores. *Heart*. May 2014:1-7.

53. Biancari F, Asim Mahar MA, Kangasniemi O-P. CHADS2 and CHA2DS2-VASc scores for prediction of immediate and late stroke after coronary artery bypass graft surgery. *J Stroke Cerebrovasc Dis*. 2013;22(8):1304-1311.

54. Hornero F, Martin E, Paredes F, et al. Stroke after coronary artery bypass grafting: preoperative predictive accuracies of CHADS2 and CHA2DS2VASc stroke risk stratification schemes. *J Thorac Cardiovasc Surg*. 2012;144(6):1428-1435.

55. Melgaard L, Gorst-Rasmussen A, Lane DA, Rasmussen LH, Larsen TB, Lip GYH. Assessment of the CHA 2 DS 2 -VASc Score in Predicting Ischemic Stroke, Thromboembolism, and Death in Patients With Heart Failure With and Without Atrial Fibrillation. *JAMA*. 2015;314(10):1.

56. Zuo M-L, Liu S, Chan K-H, et al. The CHADS2 and CHA 2DS 2-VASc scores predict new occurrence of atrial fibrillation and ischemic stroke. *J Interv Card Electrophysiol*. 2013;37(1):47-54.

57. Lip GYH, Lin H-J, Chien K-L, et al. Comparative assessment of published atrial fibrillation stroke risk stratification schemes for predicting stroke, in a non-atrial fibrillation population: The Chin-Shan Community Cohort Study. *Int J Cardiol*. 2013;168(1):414-419.

58. Barra S, Almeida I, Caetano F, et al. Stroke prediction with an adjusted R-CHA2DS2VASc score in a cohort of patients with a Myocardial Infarction. *Thromb Res*. 2013;132(2):293-299.

59. CAPRIE Steering Commitee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet*. 1996;348(9038):1329-1339.

60. Diener H-C, Ringleb PA, Savi P. Clopidogrel for the secondary prevention of stroke. *Expert Opin Pharmacother*. 2005;6(5):755-764.

61. Mohan KM, Wolfe CDA, Rudd AG, Heuschmann PU, Kolominsky-Rabas PL, Grieve AP. Risk and cumulative risk of stroke recurrence: a systematic review and meta-analysis. *Stroke*. 2011;42(5):1489-1494.

62. Ay H, Gungor L, Arsava EM, et al. A score to predict early risk of recurrence after ischemic stroke. *Neurology*. 2010;74(2):128-135.

63. Coull a J, Lovett JK, Rothwell PM. Population based study of early risk of stroke after transient ischaemic attack or minor stroke: implications for public education and organisation of services. *BMJ*. 2004;328(7435):326.

64. Mohan KM, Crichton SL, Grieve AP, Rudd AG, Wolfe CDA, Heuschmann PU. Frequency and predictors for the risk of stroke recurrence up to 10 years

after stroke: the South London Stroke Register. *J Neurol Neurosurg Psychiatry*. 2009;80(9):1012-1018.

65. Hardie K, Hankey GJ, Jamrozik K, Broadhurst RJ, Anderson C. Ten-year risk of first recurrent stroke and disability after first-ever stroke in the Perth Community Stroke Study. *Stroke*. 2004;35(3):731-735.

66. Lovett JK, Coull a J, Rothwell PM. Early risk of recurrence by subtype of ischemic stroke in population-based incidence studies. *Neurology*. 2004;62(4):569-573.

67. Hillen T, Coshall C, Tilling K, Rudd AG, McGovern R, Wolfe CDA. Cause of stroke recurrence is multifactorial: patterns, risk factors, and outcomes of stroke recurrence in the South London Stroke Register. *Stroke*. 2003;34(6):1457-1463.

68. van Wijk I, Kappelle LJ, van Gijn J, et al. Long-term survival and vascular event risk after transient ischaemic attack or minor ischaemic stroke: a cohort study. *Lancet (London, England)*. 2005;365(9477):2098-2104.

69. Putaala J, Haapaniemi E, Metso AJ, et al. Recurrent ischemic events in young adults after first-ever ischemic stroke. *Ann Neurol*. 2010;68(5):661-671.

70. Pennlert J, Eriksson M, Carlberg B, Wiklund P-G. Long-Term Risk and Predictors of Recurrent Stroke Beyond the Acute Phase. *Stroke*. May 2014.

71. Wolf P a., D'Agostino RB, Belanger a. J, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. *Stroke*. 1991;22(3):312-318.

72. Thompson DD, Murray GD, Dennis M, Sudlow CL, Whiteley WN. Formal and informal prediction of recurrent stroke and myocardial infarction after stroke: a systematic review and evaluation of clinical prediction models in a new cohort. *BMC Med*. 2014;12(1):58.

73. Merwick A, Albers GW, Amarenco P, et al. Addition of brain and carotid imaging to the $ABCD^2$ score to identify patients at early risk of stroke after transient ischaemic attack: a multicentre observational study. *Lancet Neurol*. 2010;9(11):1060-1069.

74. Pencina MJ, D'Agostino RB, Vasan RS. Statistical methods for assessment of added usefulness of new biomarkers. *Clin Chem Lab Med*. 2010;48(12):1703-1711.

75. Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the performance of prediction models: a framework for traditional and novel measures. *Epidemiology*. 2010;21(1):128-138.

76. Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: seven steps for development and an ABCD for validation. *Eur Heart J*. June 2014:1925-1931.

77. Maier IL, Bauerle M, Kermer P, Helms H-J, Buettner T. Risk prediction of very early recurrence, death and progression after acute ischaemic stroke. *Eur J Neurol*. 2013;20(4):599-604.

78. Rothman KJ. *Epidemiology. An Introduction*. 2nd ed. New York: Oxford University Press; 2012.

79. Satagopan JM, Ben-Porat L, Berwick M, Robson M, Kutler D, Auerbach a D. A note on competing risks in survival data analysis. *Br J Cancer*. 2004;91(7):1229-1235.

80. Andersen PK, Geskus RB, de Witte T, Putter H. Competing risks in epidemiology: possibilities and pitfalls. *Int J Epidemiol*. 2012;41(3):861-870.

81. Wolbers M, Koller MT, Witteman JCM, Steyerberg EW. Prognostic models with competing risks: methods and application to coronary risk prediction. *Epidemiology*. 2009;20(4):555-561.

82. Wildenschild C, Mehnert F, Thomsen RW, et al. Registration of acute stroke: validity in the Danish Stroke Registry and the Danish National Registry of Patients. *Clin Epidemiol*. 2013;6:27-36.

83. Ntaios G, Lip GYH, Lambrou D, et al. Leukoaraiosis and stroke recurrence risk in patients with and without atrial fibrillation. *Neurology*. 2015;84(12):1213-1219.

84. Overvad TF, Rasmussen LH, Skjøth F, et al. Female sex as a risk factor for thromboembolism and death in patients with incident atrial fibrillation. The prospective Danish Diet, Cancer and Health study. *Thromb Haemost*. 2014;112(4):789-795.

85. Levy D, Kenchaiah S, Larson MG, et al. Long-term trends in the incidence of and survival with heart failure. *N Engl J Med*. 2002;347(18):1397-1402.

86. Caro J, Migliaccio-Walle K, Ishak KJ, Proskorovsky I. The morbidity and mortality following a diagnosis of peripheral arterial disease: long-term follow-up of a large database. *BMC Cardiovasc Disord*. 2005;5:14.

87. Aune E, Røislien J, Mathisen M, Thelle DS, Otterstad J. The "smoker's paradox" in patients with acute coronary syndrome: a systematic review. *BMC Med*. 2011;9(1):97.

88. Gourlay SG, Rundle AC, Barron H V. Smoking and mortality following acute myocardial infarction: results from the National Registry of Myocardial Infarction 2 (NRMI 2). *Nicotine Tob Res*. 2002;4(1):101-107.

89. Ruiz-Bailén M, de Hoyos EA, Reina-Toral A, Torres-Ruiz JM, Alvarez-Bueno M, Gómez Jiménez FJ. Paradoxical effect of smoking in the Spanish population with acute myocardial infarction or unstable angina: results of the

ARIAM Register. *Chest*. 2004;125(3):831-840.

90. Vermeer SE, Hollander M, van Dijk EJ, Hofman A, Koudstaal PJ, Breteler MMB. Silent brain infarcts and white matter lesions increase stroke risk in the general population: the Rotterdam Scan Study. *Stroke*. 2003;34(5):1126-1129.

91. Kuller LH, Longstreth WT, Arnold AM, Bernick C, Bryan RN, Beauchamp NJ. White matter hyperintensity on cranial magnetic resonance imaging: a predictor of stroke. *Stroke*. 2004;35(8):1821-1825.

92. Bokura H, Kobayashi S, Yamaguchi S, et al. Silent brain infarction and subcortical white matter lesions increase the risk of stroke and mortality: a prospective cohort study. *J Stroke Cerebrovasc Dis*. 2006;15(2):57-63.

93. Poels MMF, Steyerberg EW, Wieberdink RG, et al. Assessment of cerebral small vessel disease predicts individual stroke risk. *J Neurol Neurosurg Psychiatry*. 2012;83(12):1174-1179.

94. Kuller LH, Arnold AM, Longstreth WT, et al. White matter grade and ventricular volume on brain MRI as markers of longevity in the cardiovascular health study. *Neurobiol Aging*. 2007;28(9):1307-1315.

95. Melkas S, Sibolt G, Oksala NKJ, et al. Extensive white matter changes predict stroke recurrence up to 5 years after a first-ever ischemic stroke. *Cerebrovasc Dis*. 2012;34(3):191-198.

96. Putaala J, Haapaniemi E, Kurkinen M, Salonen O, Kaste M, Tatlisumak T. Silent brain infarcts, leukoaraiosis, and long-term prognosis in young ischemic stroke patients. *Neurology*. 2011;76(20):1742-1749.

97. Miyao S, Takano A, Teramoto J, Takahashi A. Leukoaraiosis in relation to prognosis for patients with lacunar infarction. *Stroke*. 1992;23(10):1434-1438.

98. van Swieten JC, Kappelle LJ, Algra A, van Latum JC, Koudstaal PJ, van Gijn J. Hypodensity of the cerebral white matter in patients with transient ischemic attack or minor stroke: influence on the rate of subsequent stroke. Dutch TIA Trial Study Group. *Ann Neurol*. 1992;32(2):177-183.

99. Clavier I, Hommel M, Besson G, Noèlle B, Perret JE. Long-term prognosis of symptomatic lacunar infarcts. A hospital-based study. *Stroke*. 1994;25(10):2005-2009.

100. Podgorska A, Hier DB, Pytlewski A, Czlonkowska A. Leukoaraiosis and stroke outcome. *J Stroke Cerebrovasc Dis*. 2002;11(6):336-340.

101. Streifler JY, Eliasziw M, Benavente OR, et al. Prognostic importance of leukoaraiosis in patients with symptomatic internal carotid artery stenosis. *Stroke*. 2002;33(6):1651-1655.

102. Hénon H, Vroylandt P, Durieu I, Pasquier F, Leys D. Leukoaraiosis more than dementia is a predictor of stroke recurrence. *Stroke*. 2003;34(12):2935-2940.

103. Appelros P, Samuelsson M, Lindell D. Lacunar infarcts: functional and cognitive outcomes at five years in relation to MRI findings. *Cerebrovasc Dis*. 2005;20(1):34-40.

104. Fu JH, Lu CZ, Hong Z, Dong Q, Luo Y, Wong KS. Extent of white matter lesions is related to acute subcortical infarcts and predicts further stroke risk in patients with first ever ischaemic stroke. *J Neurol Neurosurg Psychiatry*. 2005;76(6):793-796.

105. Kim G-M, Park K-Y, Avery R, et al. Extensive Leukoaraiosis Is Associated With High Early Risk of Recurrence After Ischemic Stroke. *Stroke*. 2014;45(2):479-485.

106. Kumral E, Güllüoğlu H, Alakbarova N, et al. Association of Leukoaraiosis with Stroke Recurrence within 5 Years after Initial Stroke. *J Stroke Cerebrovasc Dis*. 2015;24(3):573-582.

107. Ikram MA, Vernooij MW, Vrooman HA, Hofman A, Breteler MMB. Brain tissue volumes and small vessel disease in relation to the risk of mortality. *Neurobiol Aging*. 2009;30(3):450-456.

108. Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. *Bmj*. 2010;341(jul26 1):c3666-c3666.

109. Oksala NKJ, Oksala a, Pohjasvaara T, et al. Age related white matter changes predict stroke death in long term follow-up. *J Neurol Neurosurg Psychiatry*. 2009;80(7):762-766.

110. Jørgensen HS, Nakayama H, Raaschou HO, Olsen TS. Leukoaraiosis in stroke patients. The Copenhagen Stroke Study. *Stroke*. 1995;26(4):588-592.

111. D'Agostino R. Risk prediction and finding new independent prognostic factors. *J Hypertens*. 2006;24(4):643-645.

112. Fazekas F, Chawluk J, Alavi A, Hurtig H, Zimmerman R. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *Am J Roentgenol*. 1987;149(2):351-356.

113. Michael J. Pencina, Ralph B. D'Agostino Sr RBDJ and RSV. Evaluating the added predictive ability of a newmarker: From area under the ROC curve to reclassification and beyond. *Stat Med*. 2008;27(2):157-172.

114. Kerr KF, Wang Z, Janes H, McClelland RL, Psaty BM, Pepe MS. Net reclassification indices for evaluating risk prediction instruments: a critical review. *Epidemiology*. 2014;25(1):114-121.

115. Fazekas FB. CT and MRI rating of white matter lesions. *Cerebrovasc Dis*. 2002;13 Suppl 2.

116. Wahlund LO, Barkhof F, Fazekas F, et al. A new rating scale for age-related white matter changes applicable to MRI and CT. *Stroke*. 2001;32(6):1318-1322.

117. Hesselink JR. Differential diagnostic approach to MR imaging of white matter diseases. *Top Magn Reson Imaging*. 2006;17(4):243-263.

118. Barkhof F, Scheltens P. Imaging of white matter lesions. *Cerebrovasc Dis*. 2002;13 Suppl 2(Suppl. 2):21-30.

119. Schmidt R, Schmidt H, Haybaeck J, et al. Heterogeneity in age-related white matter changes. *Acta Neuropathol*. 2011;122(2):171-185.

120. Valdés Hernández M del C, Maconick LC, Muñoz Maniega S, et al. A comparison of location of acute symptomatic vs. "silent" small vessel lesions. *Int J Stroke*. 2015;10(7):1044-1050.

121. Potter GM, Doubal FN, Jackson C a, et al. Counting cavitating lacunes underestimates the burden of lacunar infarction. *Stroke*. 2010;41(2):267-272.

122. de Jong G, Kessels F, Lodder J. Two Types of Lacunar Infarcts: Further Arguments From a Study on Prognosis. *Stroke*. 2002;33(8):2072-2076.

123. EAFT Study Group. Silent brain infarction in nonrheumatic atrial fibrillation. EAFT Study Group. European Atrial Fibrillation Trial. *Neurology*. 1996;46(1):159-165.

124. Weber R, Weimar C, Wanke I, et al. Risk of recurrent stroke in patients with silent brain infarction in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) imaging substudy. *Stroke*. 2012;43(2):350-355.

125. Boon A, Lodder J, Heuts-van Raak L, Kessels F. Silent brain infarcts in 755 consecutive patients with a first-ever supratentorial ischemic stroke. Relationship with index-stroke subtype, vascular risk factors, and mortality. *Stroke*. 1994;25(12):2384-2390.

126. Jørgensen HS, Nakayama H, Raaschou HO, Gam J, Olsen TS. Silent infarction in acute stroke patients. Prevalence, localization, risk factors, and clinical significance: the Copenhagen Stroke Study. *Stroke*. 1994;25(1):97-104.

127. Brainin M, McShane LM, Steiner M, Dachenhausen A, Seiser A. Silent brain infarcts and transient ischemic attacks. A three-year study of first-ever ischemic stroke patients: the Klosterneuburg Stroke Data Bank. *Stroke*. 1995;26(8):1348-1352.

128. Potter GM, Chappell FM, Morris Z, Wardlaw JM. Cerebral Perivascular Spaces Visible on Magnetic Resonance Imaging: Development of a

Qualitative Rating Scale and its Observer Reliability. *Cerebrovasc Dis*. 2015;39(3-4):224-231.

129. Khan U, Porteous L, Hassan A, Markus HS. Risk factor profile of cerebral small vessel disease and its subtypes. *J Neurol Neurosurg Psychiatry*. 2007;78(7):702-706.

130. Juul S. *Epidemiologi Og Evidens*. 2. udgave. København: Munksgaard; 2012.

131. Wardlaw JM, Ferguson KJ. 20 standard MR scans with validated ratings on several white matter rating scales. University of Edinburgh. www.sbirc.ed.ac.uk. Accessed 8 July 2014.

132. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health*. 2011;39(7 Suppl):22-25.

133. Johnsen SP, Overvad K, Sørensen HT, Tjønneland A, Husted SE. Predictive value of stroke and transient ischemic attack discharge diagnoses in The Danish National Registry of Patients. *J Clin Epidemiol*. 2002;55(6):602-607.

134. Krarup L-H, Boysen G, Janjua H, Prescott E, Truelsen T. Validity of stroke diagnoses in a National Register of Patients. *Neuroepidemiology*. 2007;28(3):150-154.

135. Joensen AM, Jensen MK, Overvad K, et al. Predictive values of acute coronary syndrome discharge diagnoses differed in the Danish National Patient Registry. *J Clin Epidemiol*. 2009;62(2):188-194.

136. Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2008.

137. Helweg-Larsen K. The Danish Register of Causes of Death. *Scand J Public Health*. 2011;39(7 Suppl):26-29.

138. D'Agostino RB, Wolf PA, Belanger AJ, Kannel WB. Stroke risk profile: adjustment for antihypertensive medication. The Framingham Study. *Stroke*. 1994;25(1):40-43.

139. Staals J, Makin SDJ, Doubal FN, Dennis MS, Wardlaw JM. Stroke subtype, vascular risk factors, and total MRI brain small-vessel disease burden. *Neurology*. 2014;83(14):1228-1234.

140. Jickling GC, Chen C. Rating total cerebral small-vessel disease: does it add up? *Neurology*. 2014;83(14):1224-1225.

141. Hankey GJ, Slattery JM, Warlow CP. Transient ischaemic attacks: which patients are at high (and low) risk of serious vascular events? *J Neurol Neurosurg Psychiatry*. 1992;55(8):640-652.

142. The Dutch TIA Trial Study Group. Predictors of major vascular events in patients with a transient ischemic attack or nondisabling stroke. The Dutch

TIA Trial Study Group. *Stroke*. 1993;24(4):527-531.

143. Johnston SC, Gress DR, Browner WS, Sidney S. Short-term prognosis after emergency department diagnosis of TIA. *JAMA*. 2000;284(22):2901-2906.

144. Kernan WN, Viscoli CM, Brass LM, et al. The stroke prognosis instrument II (SPI-II): A clinical prediction instrument for patients with transient ischemia and nondisabling ischemic stroke. *Stroke*. 2000;31(2):456-462.

145. Pezzini A, Grassi M, Del Zotto E, et al. Common genetic markers and prediction of recurrent events after ischemic stroke in young adults. *Neurology*. 2009;73(9):717-723.

146. Kamouchi M, Kumagai N, Okada Y, Origasa H, Yamaguchi T, Kitazono T. Risk score for predicting recurrence in patients with ischemic stroke: the Fukuoka stroke risk score for Japanese. *Cerebrovasc Dis*. 2012;34(5-6):351-357.

147. Cámara AG de la, Arche JFV, Paloma Ferrando Vivas, et al. Recurrence after a First- ever Ischemic Stroke Development of a Clinical Prediction Rule. *Res Neurol An Int J*. 2013;2013:1-13.

148. Rothwell PM, Giles MF, Flossmann E, et al. A simple score (ABCD) to identify individuals at high early risk of stroke after transient ischaemic attack. *Lancet*. 366(9479):29-36.

149. Johnston SC, Rothwell PM, Nguyen-Huynh MN, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *Lancet*. 2007;369(9558):283-292.

150. Kernan WN, Horwitz RI, Brass LM, Viscoli CM, Taylor KJ. A prognostic system for transient ischemia or minor stroke. *Ann Intern Med*. 1991;114(7):552-557.

151. Gioia LC, Tollard É, Dubuc V, et al. Silent ischemic lesions in young adults with first stroke are associated with recurrent stroke. *Neurology*. 2012;79(12):1208-1214.

APPENDICES

Appendix A: The Essen Stroke Risk Score

Appendix B: Risk Score Schemes in Stroke

Appendix C: Figures of Cumulative Risk of Recurrent Ischemic Stroke

Appendix D: Study 1

Appendix E: Study 2

Appendix F: Study 3

APPENDIX A. THE ESSEN STROKE RISK SCORE

The Essen Stroke Risk Score.

Risk factors	Points
Age < 65 years	0
Age 65-75 years	1
Age > 75 years	2
Hypertension	1
Diabetes	1
Previous MI	1
Other cardiovascular disease (except MI and AF)	1
Peripheral arterial disease	1
Smoking	1
Additional TIA or ischemic stroke in addition to qualifying event	1

Abbreviations: MI, myocardial infarction; AF, atrial fibrillation; TIA, transient ischemic attack.

APPENDIX B. RISK SCORE SCHEMES IN STROKE

Risk score schemes derived from TIA and stroke cohorts with multivariate models for stroke risk prediction.

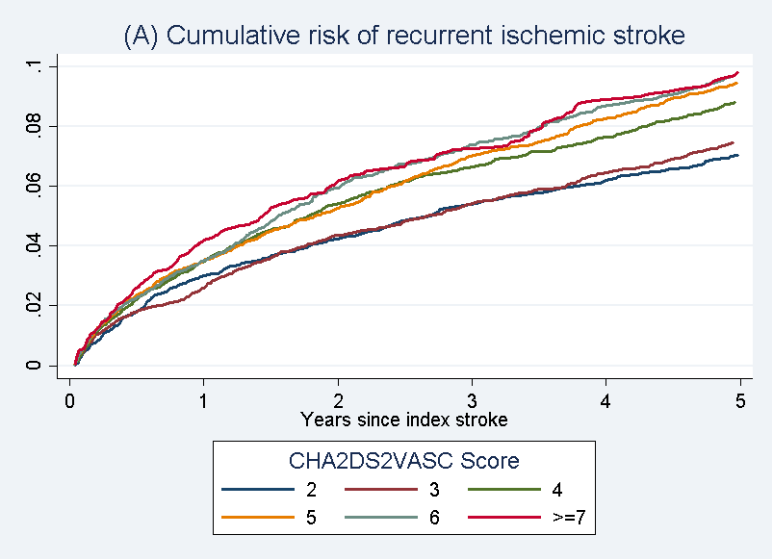
Study	Population	Endpoint	Risk Factors
Hankey[141] (1992)	TIA	Ischemic stroke within 1 or 5 years	Regression model including: Age; sex; amaurosis fugax versus brain TIA; vascular territory of TIA (carotid or vertebral); number of TIAs; PAD; left ventricular hypertrophy (on ECG); residual neurological signs
The Dutch TIA Trial[142] (1993)	TIA and ischemic stroke	Stroke or major vascular events within 4 years	Regression model including: Age >65 years; sex; dysarthria; multiple attacks; symptoms >6 weeks; hypertension; diabetes; prior MI; angina pectoris; intermittent claudication; hematocrit; CT characteristics (borders zone infarct, other infarcts, white matter lesions); ECG characteristics (anteroseptal infarct, ST depression, increased tem P wave, left ventricular hypertrophy)
The California Score[143] (2000)	TIA	Ischemic stroke within 90 days	Point based model: Age >60 years; diabetes; duration of TIA (>10 minutes); weakness with TIA episode; speech impairment with TIA episode
The Stroke Prognosis Instrument II (SPI-II)[144] (2000)	TIA and ischemic stroke	Stroke or death within 2 years	Point based model: Congestive heart failure (3 points); diabetes (3 points); prior stroke (3 points); age >70 years (2 points); stroke as index event (not TIA) (2 points); hypertension (1 point); coronary artery disease (1 point)
Essen Stroke Risk Score[60] (2005)	TIA and ischemic stroke	Ischemic stroke within 1-3 years	Point based model: 1 point for each factor: Age (65-75 years: 1 point; >75 years: 2 points), hypertension, diabetes, other CV disease (except MI and AF), PAD, smoking, previous TIA or ischemic stroke (in addition to qualifying event)
LiLAC Study Group[68] (2005)	TIA or ischemic stroke	Ischemic stroke within 10 years	Regression model including: Sex; age; intermittent claudication; diabetes; hypertension; stroke versus TIA; paresis; dysarthria; white matter lesion (on CT); infarct (on CT); ST-depression (on ECG)

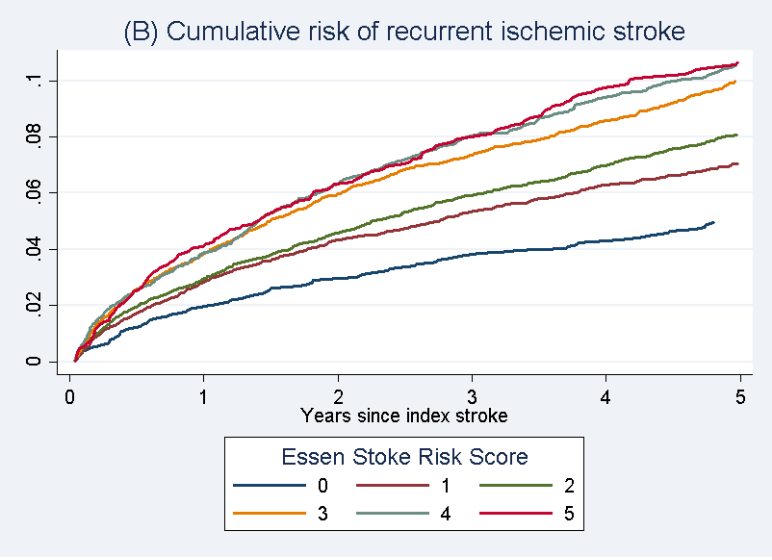
Pezzini[145] (2009)	Incident ischemic stroke; age 15-49 years	Ischemic stroke, TIA, or MI within 4 years	Point-based model: Hypertension; diabetes; smoking; hypercholesterolemia; migraine; family history of stroke; model enhanced with genetic factors.
ABCD^3-I Score[73] (2010)	TIA	Ischemic stroke within 2, 7, 28, and 90 days	Point-based model: Age ≥60 years; BP ≥149/90 mm Hg; clinical features: unilateral weakness, aphasia without weakness; duration: ≥60 minutes or 10-59 minutes; diabetes; dual TIA (within 7 days); same-sided >49% internal carotid artery stenosis; MRI DWI hyperintensity
Putaala[69] (2010)	Incident ischemic stroke; age 15-49 years	Ischemic stroke within 5 years	Regressions models (four) including: Age; sex; smoking; hypertension; heart failure; coronary heart disease; previous TIA; PAD; type 1 diabetes; number of the above risk factors; stroke etiology
RRE-90[62] (2010)	Ischemic stroke	Ischemic stroke within 90 days	Regression models (two) including: Etiologic stroke subtype; prior history of TIA or stroke; topography of index stroke; age; distribution of brain infarcts
The Fukuoka Stroke Risk Score[146] for Japanese (2012)	Ischemic stroke	Ischemic stroke within 1 year	Point-based model: Age (65-74 years, 1 point; ≥ 75 years, 2 points); hypertension, diabetes, smoking, atrial fibrillation, chronic kidney disease, nonlacunar stroke, previous ischemic stroke. Separate data on non-cardioembolic stroke.
Suzuki[29] (2012)	Non-cardioembolic ischemic stroke; age ≥45 years	Ischemic stroke within 1 year	Regression model including: Age; sex; hypertension; hyperlipidemia; diabetes; waist circumference; previous stroke; modified Rankin scale
Cámara[147] (2013)	Incident ischemic stroke	Ischemic stroke within 2 years	Algorithm including: Age <70 versus age >70; hypertensive cardiomyopathy / left ventricular hypertrophy; coronary heart disease; anticoagulant therapy; chronic kidney disease
Sumi[30] (2013)	Non-cardioembolic ischemic stroke; age ≥45 years	Ischemic stroke within 1 year	Regression model based on the Essen Stroke Risk Score with addition of waist circumference, stroke subtype, and sex

Abbreviations: TIA, transient ischemic attack; PAD, peripheral arterial disease; ECG, electrocardiogram; MI, myocardial infarction; CT, computed tomography; CV, cardiovascular; AF, atrial fibrillation; MRI, magnetic resonance imaging; DWI, diffusion weighted imaging. The ABCD^3-I score was developed from the ABCD[148] Score and the ABCD^2 [149] Score (not shown). The Stroke Prognosis Instrument II (SPI-II) was developed from the SPI-I[150] (not shown).

APPENDIX C. FIGURES OF CUMULATIVE RISK OF RECURRENT ISCHEMIC STROKE

Cumulative risk of recurrent ischemic stroke stratified into six groups on the CHA_2DS_2VASc score (A) and the Essen Stroke Risk Score (B). The data source is the study population of Study 1.





APPENDIX D. STUDY 1

Recurrent Stroke

The Value of the CHA_2DS_2VASc Score and the Essen Stroke Risk Score in a Nationwide Stroke Cohort

Søren Due Andersen, MD; Anders Gorst-Rasmussen, MSc, PhD; Gregory Y.H. Lip, MD; Flemming W. Bach, MD, DMSc; Torben Bjerregaard Larsen, MD, PhD

Background and Purpose—The CHA_2DS_2VASc score and the Essen Stroke Risk Score are respectively used for risk stratification in patients with atrial fibrillation and in patients with cerebrovascular incidents. We aimed to test the ability of the 2 scores to predict stroke recurrence, death, and cardiovascular events (stroke, transient ischemic attack, myocardial infarction, or arterial thromboembolism) in a nationwide Danish cohort study, among patients with incident ischemic stroke and no atrial fibrillation.

Methods—We conducted a registry-based study in patients with incident ischemic stroke and no atrial fibrillation. Patients were stratified according to the CHA_2DS_2VASc score and the Essen Stroke Risk Score and were followed up until stroke recurrence or death. We estimated stratified incidence rates and hazard ratios and calculated the cumulative risks.

Results—42 182 patients with incident ischemic stroke with median age 70.1 years were included. The overall 1-year incidence rates of recurrent stroke, death, and cardiovascular events were 3.6%, 10.5%, and 6.7%, respectively. The incidence rates, the hazard ratios, and the cumulative risk of all outcomes increased with increasing risk scores. C-statistics for both risk scores were around 0.55 for 1-year stroke recurrence and cardiovascular events and correspondingly for death around 0.67 for both scores.

Conclusions—In this cohort of non–atrial fibrillation patients with incident ischemic stroke, increasing CHA_2DS_2VASc score and Essen Stroke Risk Score was associated with increasing risk of recurrent stroke, death, and cardiovascular events. Their discriminatory performance was modest and further refinements are required for clinical application. **(*Stroke*. 2015;46:2491-2497. DOI: 10.1161/STROKEAHA.115.009912.)**

Key Words: CHA_2DS_2VASc score ■ Essen Stroke Risk Score ■ risk factors ■ stroke ■ stroke recurrence

Various clinical scoring systems have been developed for the risk stratification in cardiovascular and stroke medicine. The $CHADS_2$[1] and, more recently, the CHA_2DS_2VASc[2] scores are based on well-recognized risk factors for stroke in atrial fibrillation (AF), including congestive heart failure, hypertension, age ≥75 years (2 points), diabetes mellitus, previous stroke or transient ischemic attack (2 points), vascular disease, age 65 to 74 years, and sex class (female). The scores have been validated in various cohorts[3,4] and have become widely used for ischemic stroke risk stratification in patients with AF because of their simplicity.

To extend the possible application of these scores, there is some interest in validating the scores in non-AF patient populations. The $CHADS_2$ and the CHA_2DS_2VASc scores have been shown to be associated with the risk of stroke in non-AF patients with ischemic heart disease,[5,6] in patients undergoing coronary artery bypass grafting,[7,8] in patients with acute coronary syndrome,[9] and in addition, the scores hold promise for stroke and thromboembolism risk assessment in the general population.[10]

Risk stratification is of particular interest in patients with ischemic stroke as they are at high risk of a stroke recurrence (18% over a 5-year period[11,12]), and the recurrence risk is nonuniform across the population. A study based on the Athens Stroke Registry[13] reported that the $CHADS_2$ and the CHA_2DS_2VASc scores predict recurrent stroke and death in non-AF stroke patients. How these findings replicate in other patient populations is unknown. In addition, it is of interest to assess how the scores compare to risk scores developed specifically for the population of stroke patients. The Essen

Received April 29, 2015; final revision received June 13, 2015; accepted June 18, 2015.

From the Department of Neurology (S.D.A., F.W.B.), Unit of Clinical Biostatistics (A.G.-R.), and Department of Cardiology (T.B.L.), Aalborg University Hospital, Aalborg, Denmark; Thrombosis Research Unit, Department of Clinical Medicine, Faculty of Health, Aalborg University, Aalborg, Denmark (S.D.A., A.G.-R., G.Y.H.L., T.B.L.); and University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, United Kingdom (G.Y.H.L.).

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.115.009912/-/DC1.

Correspondence to Torben Bjerregaard Larsen, MD, PhD, Department of Cardiology, Center for Cardiovascular Research, Aalborg University Hospital, Sdr. Skovvej 15, 9000 Aalborg, Denmark. E-mail tobl@rn.dk

Stroke Risk Score is one such risk score, which is conceptually similar to the CHA_2DS_2VASc score, in that it adds points according to presence of risk factors—1 point for each of age 65 to 75 years, age above 75 years (2 points however), hypertension, diabetes mellitus, myocardial infarction, other cardiovascular disease (except myocardial infarction and AF), peripheral arterial disease, smoking, and previous stroke or transient ischemic attack, resulting in maximum score of 9 points.[14,15]

To evaluate how the CHA_2DS_2VASc score predicts recurrent stroke, death, and cardiovascular events, and in a first-ever stroke population, and how this general score compares to the more specific Essen Stroke Risk Score, we conducted a large-scale observational cohort study using nationwide Danish registry data. We hypothesized that both risk scores would exhibit comparable associations with the risk of stroke recurrence, death, and cardiovascular events.

Methods

Registry Data Sources

The study was based on The Danish Stroke Registry, The Danish National Patient Registry, The National Prescription Registry, and The Danish Civil Registration System. All 4 registries cover the entire Danish population, and linkage was facilitated via the unique personal identification number assigned to all Danish residents.

The Danish Stroke Registry was established in 2003. It is mandatory for all Danish hospital departments treating stroke patients to report a standardized set of data to the registry, including diagnosis and various clinical variables, such as selected comorbidities and smoking habits.[16] The Danish National Patient Registry[17] has registered all hospital admissions with corresponding discharge diagnoses since 1977. Up to 1993, all diagnoses were coded according to the 8th revision of the International Classification of Diseases (ICD-8), and since 1994, all diagnoses are coded according to the ICD-10. The National Prescription Registry[18] holds data on all prescriptions dispensed from Danish pharmacies since 1994, coded according to the Anatomic Therapeutic Chemical Classification System. Finally, The Danish Civil Registration System contains information on date of birth, sex, migration, and vital status of all citizens.[19]

Study Population

The study population consisted of all patients aged 18 years or above, registered in The Danish Stroke Registry with an incident ischemic stroke (ICD-10 codes I63 or I64) in the period January 1, 2003, and December 31, 2012 (index stroke). The diagnosis of stroke in The Danish Stroke Registry is based on the judgment of the treating physician(s). This judgment is based on clinical and neuroimaging information gathered during the admission. The sensitivity of a stroke diagnosis has previously been shown to be 91% to 97%.[20] To include only patients with incident stroke, we identified the first occurrence of registration of ischemic stroke for each patient in the registry. If this record stated that the patient had experienced a previous stroke (judged by the treating physician based on the available information: medical files, previous neuroimaging, patients, or proxy self-report), the patient was excluded. Patients with AF and patients who died <14 days after the index stroke were excluded. To capture AF patients not diagnosed at a hospital, patients prescribed oral anticoagulants (warfarin, phenprocoumon, dabigatran, rivaroxaban, and apixaban) within 2 years before the index stroke were excluded.

To investigate potential differences between patients on secondary stroke prevention medications and the whole cohort, we identified a subgroup of patients treated with antiplatelet drugs (aspirin, clopidogrel, and dipyridamole) and statins. Treatment with these drugs was defined as a claimed prescription of both drugs in the period from 90 days before until 90 days after the index event.

Risk Scores

Based on information in the registries, the CHA_2DS_2VASc score and the Essen Stroke Risk Score were calculated for all patients at the time of admission for the incident stroke. We followed registry-based algorithms previously decribed[3] and added information from The Danish Stroke Registry. Definitions of comorbidities applied in the risk scores can be found in the online-only Data Supplement.

Outcomes

Patients were followed from the date of the index stroke and until an event of interest or death. The events of interest were recurrent ischemic stroke or a cardiovascular event. Cardiovascular events were defined as the composite of ischemic stroke, transient ischemic attack, myocardial infarction, or arterial thromboembolism. Follow-up was censored at time of emigration or end of study (December 31, 2012). Information on emigration or death was available from the Danish Civil Registration System. Cardiovascular events were identified in The Danish Stroke Registry and The Danish National Patient Registry. Recurrence of ischemic stroke was ascertained from The Danish Stroke Registry, defining recurrent stroke as admission with a new stroke after discharge for the index event >14 days after the index stroke. This restriction was used to reduce the risk of capturing double registrations of the index stroke.

Statistical Analysis

Continuous data were summarized as mean values and standard deviations and categorical data as proportions. Event rates of recurrent ischemic stroke, death, and the composite cardiovascular end point were calculated for all patients, stratified by the CHA_2DS_2VASc score and the Essen Stroke Risk Score, respectively. Hazard ratios based on the Cox proportional hazards model were calculated for increasing values of the CHA_2DS_2VASc score and the Essen Stroke Risk Score, setting as a reference a CHA_2DS_2VASc score of 2 and an Essen Stroke Risk Score of 0, respectively. Patients with CHA_2DS_2VASc score ≥7 were merged into one stratum, and similarly patients with Essen Stroke Risk Score ≥5 were merged into one stratum. Further, we calculated estimates of Cox proportional hazards for each of the (binary) components comprised in the 2 risk scores.

The cumulative risk of stroke and cardiovascular events were calculated using the Aalen–Johansen estimator, taking into account the competing risk of death. The cumulative risk of death was calculated using the standard Kaplan–Meier estimator. The discriminatory performance of the scores was assessed with C-statistics, taking into account competing risks of death.[21] Negative predictive values (the proportion of patients with a score below the cut-off who remained event-free and alive during follow up) were calculated for the end points of stroke and cardiovascular events, with cutoff values of 2 (CHA_2DS_2VASc) and 0 (Essen Stroke Risk Score), respectively.

We performed similar analyses for the subgroup of patients treated with antiplatelet drugs and statins.

Analyses were performed using Stata version 13 (Stata Corporation, College Station, TX). The study was performed and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.

Ethics

The study was approved by the Danish Data Protection Agency (File No. 2012-41-0633). In Denmark, no ethical approval is required for anonymous registry studies.

Results

In The Danish Stroke Registry, we identified 56 682 patients ≥18 years with incident ischemic stroke in the period January 1, 2003, to December 31, 2012. We excluded 3791 patients who died within 14 days after the index event, 9981 patients with AF, and 728 patients prescribed oral anticoagulants

within 2 years before the date of the index stroke. Hence, the study cohort consisted of 42 182 patients with first-ever ischemic stroke and no AF.

Baseline characteristics of the cohort are shown in Table 1. Patients were followed up for an average of 3.5 (standard deviation [SD] 2.7) years. Based on the CHA_2DS_2VASc score, all patients were assigned 2 points for the index stroke, resulting in a mean score of 4.3 (SD 1.4). The mean Essen Stroke Risk Score was 2.4 (SD 1.4).

The overall incidence rates of recurrent stroke, death, and cardiovascular events during the first year of follow up were 3.6%, 10.5%, and 6.7% respectively. The corresponding overall incidence rates during the first 5 years of follow-up were 2.4%, 7.1%, and 4.3% per year, respectively. The stratified incidence rates are shown in Table 2. In the Cox proportional hazard analyses, the hazard ratios increased with increasing risk scores as shown in Table 3. Correspondingly, the cumulative risk of the outcomes increased with increasing risk score as shown in Figures 1 and 2.

Cox proportional hazard analyses for the single components of the scores are found in Table I in the online-only Data Supplement. All components, except for female sex, were positively associated with the outcome of stroke recurrence. The strongest predictor of stroke recurrence was peripheral arterial disease. All factors were positively associated with the risk of death, except for smoking.

The Essen Stroke Risk Score had a marginally better discriminatory performance in relation to stroke recurrence and cardiovascular event prediction than the CHA_2DS_2VASc score (Table 4), whereas the opposite was true regarding the prediction of death. Similarly, the negative predictive values for stroke recurrence and cardiovascular events with a score of 2 as cutoff value were marginally higher for the Essen Stroke Risk Score as shown in Table II in the online-only Data Supplement.

The subgroup treated with antiplatelet drugs and statins comprised 24 654 patients with a median age of 68.7 years (interquartile range 17.4 years), mean CHA_2DS_2VASc score 4.3 (SD 1.4), and mean Essen Stroke Risk Score 2.5 (SD 1.4). The overall incidence rates of recurrent stroke, death, and cardiovascular events during the first year of follow-up were 3.6%, 9.2%, and 5.5% respectively. The corresponding overall incidence rates during the first 5 years of follow-up were 2.3%, 7.1%, and 4.5% per year, respectively. The stratified analyses are shown in Tables III and IV in the online-only Data Supplement. C-statistics for the subgroup (not shown) and the whole cohort were comparable.

Discussion

In this cohort study, we investigated the performance of the CHA_2DS_2VASc score and the Essen Stroke Risk Score for predicting stroke, death, and cardiovascular events in a nationwide cohort of non-AF patients with incident ischemic stroke. We found that increasing values of the CHA_2DS_2VASc score and the Essen Stroke Risk Score were associated with an increased risk of all 3 outcomes. The scores performed reasonably well in the prediction of survival free of stroke or cardiovascular events with negative predictive values for the lowest possible score around 0.95 and 0.85 (1-year and 5-year follow-up, respectively) for both scores. When taking into account the competing risks of death, the discriminatory performance in stroke recurrence and cardiovascular events was modest, with C-statistics around 0.55 for both scores.

In accordance with previous studies in non-AF cohorts,[5,6] we demonstrated increasing stroke risk with increasing CHA_2DS_2VASc score, and we found similar results for the Essen Stroke Risk Score. However, in this cohort of patients with incident ischemic stroke, important findings differentiate it from the non-stroke cohorts. First, the baseline incidence rates of stroke are considerably higher in our cohort. With the lowest possible scores, we find incidence rates of recurrent stroke of 2.0% per year for the Essen Stroke Risk Score (score of 0) and of 3.1% per year for the CHA_2DS_2VASc (score of 2). In The Heart &

Table 1. Baseline Characteristics

Patients, n	42 182
Age, y	
Median	70.1
Interquartile range	19.3
Age >65 y, %	63.4
Age >75 y, %	37.1
Female sex, %	45.7
Congestive heart failure, %	2.3
Hypertension, %	50.5
Diabetes mellitus, %	13.5
Vascular disease, %	14.2
Previous myocardial infarction, %	5.2
Peripheral arterial disease, %	7.4
Other heart disease, %	4.4
Smoking (current or previous), %	57.2
Previous TIA, %	4.7
CHA_2DS_2VASc score, mean (SD)	4.3 (1.4)
CHA_2DS_2VASc score, %	
2	11.9
3	20.8
4	23.4
5	22.4
6	15.7
≥7	5.8
Essen Stroke Risk Score, mean (SD)	2.4 (1.4)
Essen Stroke Risk Score, %	
0	6.3
1	20.8
2	26.3
3	25.9
4	14.1
≥5	6.8

CHA_2DS_2VASc indicates congestive heart failure, hypertension, age ≥75 y (2 points), diabetes mellitus, previous stroke or transient ischemic attack (TIA; 2 points), vascular disease, age 65–74 y, and sex class (female); SD, standard deviation; and TIA, transient ischemic attack.

Table 2. One- and 5-year Incidence Rates per 100 Person-Years of Stroke, Death, and Cardiovascular Events, Stratified by the CHA_2DS_2VASc Score and the Essen Stroke Risk Score

	1-y Rates						5-y Rates					
	Stroke		Death		Cardiovascular Events		Stroke		Death		Cardiovascular Events	
CHA_2DS_2VASc Score	Events, n	Rate	Events, n	Rate	Events, n	Rate	Events, n	Rate	Events, n	Rate	Events, n	Rate
2	143	3.1	119	2.6	230	5.1	281	1.7	335	1.9	455	2.8
3	215	2.7	292	3.6	405	5.2	506	1.8	779	2.7	900	3.3
4	325	3.8	764	8.7	602	7.1	686	2.4	1825	6.0	1244	4.5
5	315	4.0	1130	13.9	535	6.8	701	2.7	2688	10.0	1175	4.7
6	219	4.1	1082	19.7	418	7.9	499	3.1	2289	13.5	891	5.7
≥7	95	5.0	507	26.2	192	10.3	185	3.5	1026	18.4	367	7.2
Essen Stroke Risk Score												
0	49	2.0	68	2.8	88	3.7	104	1.2	146	1.6	188	2.1
1	234	3.0	293	3.6	417	5.3	491	1.7	733	2.5	850	3.1
2	309	3.2	921	9.4	564	5.9	702	2.1	2130	6.2	1226	3.9
3	396	4.3	1316	14.0	666	7.4	858	2.9	3071	9.9	1418	5.0
4	216	4.4	826	16.6	407	8.5	480	3.3	1862	12.0	867	6.2
≥5	108	4.7	470	20.2	240	10.8	223	3.6	1000	15.2	483	8.2

Cardiovascular events represent the composite end point of stroke, transient ischemic attack, myocardial infarction, or arterial thromboembolism. CHA_2DS_2VASc indicates congestive heart failure, hypertension, age ≥75 y (2 points), diabetes mellitus, previous stroke or transient ischemic attack (2 points), vascular disease, age 65–74 y, and sex class (female).

Soul Cohort[5] of patients with stable coronary heart disease, the annual incidence rate of stroke and transient ischemic attack was 0.9% for a $CHADS_2$ score of 2. In their study on patients with acute coronary syndrome, Mitchell et al[6] reported an annual incidence rate of stroke below 1% for all values of the CHA_2DS_2VASc score (stratified as 1, 2, 3, and ≥4), except for previous stroke or transient ischemic attack, which resulted in an annual stroke incidence rate of 1.54%, which is comparable to the baseline risk in our study. Second, the difference in stroke incidence rate between the lowest and the highest risk score is limited, which is reflected in the low hazard ratios, which only in the Essen

Table 3. Cox Proportional Hazard Analysis Showing 1- and 5-year Hazard Ratios of Stroke, Death, and Cardiovascular Events Stratified by the CHA_2DS_2VASc Score and the Essen Stroke Risk Score

	1-y Hazard Ratio			5-y Hazard Ratio		
	Stroke	Death	Cardiovascular Events	Stroke	Death	Cardiovascular Events
CHA_2DS_2VASc Score						
2	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
3	0.87 (0.70–1.07)	1.41 (1.14–1.75)	1.02 (0.86–1.19)	1.06 (0.91–1.22)	1.37 (1.20–1.55)	1.16 (1.04–1.30)
4	1.20 (0.98–1.46)	3.36 (2.77–4.07)	1.38 (1.19–1.61)	1.37 (1.19–1.57)	3.04 (2.71–3.42)	1.55 (1.39–1.72)
5	1.25 (1.02–1.52)	5.32 (4.41–6.43)	1.32 (1.13–1.54)	1.56 (1.35–1.79)	5.01 (4.48–5.62)	1.62 (1.45–1.80)
6	1.27 (1.03–1.57)	7.47 (6.18–9.03)	1.52 (1.29–2.39)	1.72 (1.48–1.99)	6.66 (5.94–7.47)	1.91 (1.71–2.14)
≥7	1.56 (1.20–2.02)	9.84 (8.06–12.02)	1.97 (1.63–2.39)	1.90 (1.58–2.29)	8.93 (7.89–10.10)	2.36 (2.05–2.71)
Essen Stroke Risk Score						
0	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
1	1.46 (1.07–1.98)	1.31 (1.00–1.70)	1.45 (1.15–1.82)	1.47 (1.19–1.82)	1.55 (1.30–1.85)	1.41 (1.21–1.65)
2	1.57 (1.16–2.13)	3.35 (2.62–4.29)	1.60 (1.25–2.01)	1.80 (1.46–2.21)	3.86 (3.26–4.56)	1.75 (1.50–2.04)
3	2.11 (1.57–2.83)	4.97 (3.90–6.34)	1.98 (1.58–2.47)	2.41 (1.97–2.96)	6.09 (5.15–7.18)	2.23 (1.91–2.59)
4	2.16 (1.58–2.94)	5.85 (4.57–7.49)	2.28 (1.81–2.87)	2.65 (2.14–3.28)	7.26 (6.14–8.60)	2.69 (2.30–3.15)
≥5	2.30 (1.64–3.22)	7.06 (5.47–9.10)	2.87 (2.24–3.66)	2.81 (2.22–3.54)	8.98 (7.55–10.69)	3.44 (2.91–4.07)

Data are hazard ratios (95% confidence intervals). Ref. indicates reference. Cardiovascular events represent the composite end point of stroke, transient ischemic attack, myocardial infarction, or arterial thromboembolism. CHA_2DS_2VASc indicates congestive heart failure, hypertension, age ≥75 y (2 points), diabetes mellitus, previous stroke or transient ischemic attack (TIA; 2 points), vascular disease, age 65–74 y, and sex class (female); and TIA, transient ischemic attack.

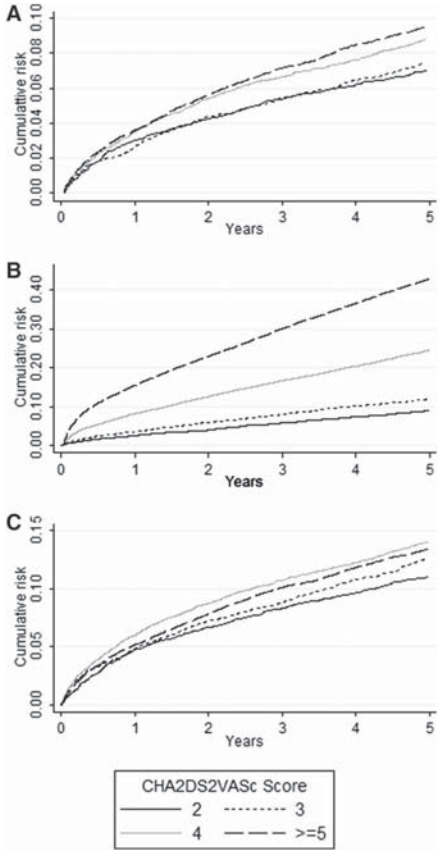


Figure 1. Five-year cumulative risk of stroke recurrence (**A**), death (**B**), and cardiovascular events (**C**) stratified by the CHA_2DS_2VASc score. The cumulative risks of stroke recurrence and cardiovascular events were assessed with death as competing risk. CHA_2DS_2VASc indicates congestive heart failure, hypertension, age ≥75 y (2 points), diabetes mellitus, previous stroke or transient ischemic attack (2 points), vascular disease, age 65–74 y, and sex class (female).

Stroke Risk Score exceed a value of 2. That means, adding further risk factors does increase the stroke risk, but only modest, as seen from a 1-year stroke recurrence hazard ratio of 1.56 (1.20–2.02) for a CHA_2DS_2VASc score ≥7. Hence, previous stroke or thromboembolism confers a much higher baseline risk, which outweighs the impact of the other risk factors. However, in AF-patients as well, it seems that previous thromboembolism plays a special role, as reported in a recent Danish study.[22] In that study, it was shown that previous thromboembolism as defined in the CHA_2DS_2VASc score adds more than the double to the total risk of stroke and other thromboembolic events than does the sum of any other 2 risk factors in the CHA_2DS_2VASc score.

We found the 5-year cumulative risks of stroke recurrence in the CHA_2DS_2VASc baseline group to be comparable to the results of the study from the Athens Stroke Registry (around 7% to 9%).[13] By contrast, in the high risk groups, we found the cumulative risk of stroke recurrence to be somewhat lower: around 10% for a CHA_2DS_2VASc score ≥5 versus almost 20% for a CHA_2DS_2VASc score ≥2 in the Greek study (they did not count the incident stroke in the score). The Greek cohort was established over a wide time span (1993–2011), possibly resulting in greater inhomogeneity in treatment and recurrence risk, but also the influence of competing risks must be considered. From the total number of deaths, which in the present study exceeds 25%, it is clear that competing risks must be taken into account to avoid overestimating the risk of stroke.[22,23]

The Essen Stroke Risk Score is marginally superior to the CHA_2DS_2VASc score in stroke recurrence prediction when assessed with the C-statistics and estimates of the negative predictive values of the lowest possible score. In the Cox regression analysis of the single components of the scores, we find that female sex is significantly protective against recurrent stroke with a hazard ratio of 0.87 (95% confidence interval, 0.78–0.98) in the first year. This explains, at least partly, the difference between the 2 scores because sex is not comprised

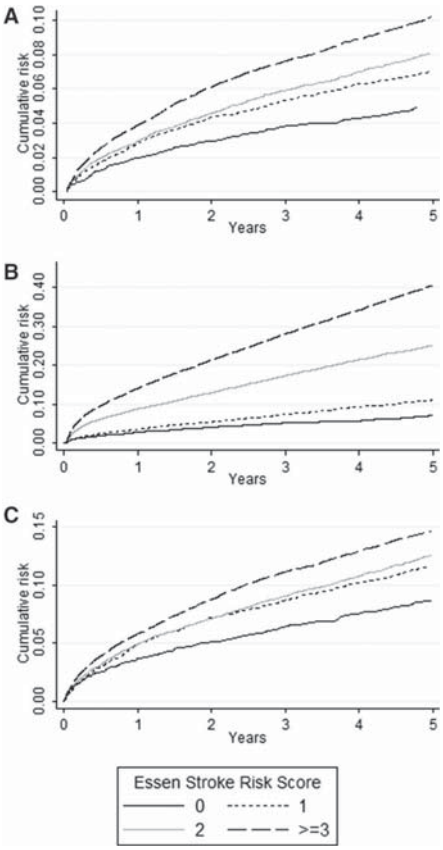


Figure 2. Five-year cumulative risk of stroke recurrence (**A**), death (**B**), and cardiovascular events (**C**) stratified by the Essen Stroke Risk Score. The cumulative risks of stroke recurrence and cardiovascular events were assessed with death as competing risk.

Table 4. C-Statistics for the CHA_2DS_2VASc Score and the Essen Stroke Risk Score

End Point		CHA_2DS_2VASc Score	Essen Stroke Risk Score
Stroke	1-year	0.52 (0.51–0.53)	0.54 (0.53–0.55)
	5-year	0.54 (0.53–0.55)	0.56 (0.55–0.57)
Death	1-year	0.68 (0.67–0.68)	0.65 (0.64–0.66)
	5-year	0.68 (0.68–0.69)	0.66 (0.66–0.67)
Cardiovascular Events	1-year	0.53 (0.52–0.54)	0.55 (0.54–0.56)
	5-year	0.55 (0.54–0.56)	0.57 (0.57–0.58)

Data are C-statistics (95% confidence intervals). C-statistics for stroke recurrence and cardiovascular events were estimated with death as competing risk. Cardiovascular events represent the composite end point of stroke, transient ischemic attack, myocardial infarction, or arterial thromboembolism. CHA_2DS_2VASc indicates congestive heart failure, hypertension, age ≥75 y (2 points), diabetes mellitus, previous stroke or transient ischemic attack (2 points), vascular disease, age 65–74 y, and sex class (female).

in the Essen Stroke Risk Score, and it emphasizes difficulties in applying the CHA_2DS_2VASc score in a non-AF cohort.

In the subgroup analyses of patients treated with antiplatelet drugs and statins, the rates of death and cardiovascular events after the first year of follow-up were marginally lower in the treatment group, but these differences disappeared after 5 years of follow up, not affecting the overall conclusion of the study.

Clearly, as shown in this study, stroke patients are at high risk of new cardiovascular events, and even at higher risk of death. The discriminatory performance of the scores in prediction of cardiovascular events is comparable to previous evaluations of The Essen Stroke Risk Score[24] and is only modest. Overall, the performance in the prediction of death is somewhat better, which may be attributable to the strong influence of age on this outcome.

Strengths and Limitations

The main strength of this study is the nationwide design resulting in a large cohort with a large number of events in all strata. Our study is limited by its observational nature based on registry data. The diagnosis of stroke relies on correct diagnosis in The Danish Stroke Registry, which has previously been validated, showing a positive predictive value of 90% of a stroke diagnosis.[20] We are not able to rule out that some cases of death could be caused by undiagnosed stroke as we do not have access to information of causes of death on all patients.

The frequency of risk factors in the cohort and the calculation of the risk scores may differ from the results of an individual assessment by a physician. However, we used a combination of previously validated algorithms[3] and information from The Danish Stroke Registry to optimize the sensitivity of our comorbidity diagnoses.

Conclusions

The CHA_2DS_2VASc score and the Essen Stroke Risk Score predicted stroke, death, and cardiovascular events in this nationwide cohort of patients with incident ischemic stroke. Future refinements of clinical risk scores are required and decision-making based on these scores may not be warranted at present. Reliable risk stratification will enable the clinician to point out high risk patients who may benefit from a more intense follow-up and a more rigorous approach to the modifiable risk factors and have consequences for the choice(s) of antithrombotic treatment.

Sources of Funding

The study was supported by a grant from the Heinrich Kopp Foundation.

Disclosures

Dr Lip has served as a consultant for Bayer, Astellas, Merck, Sanofi, BMS/Pfizer, Daiichi-Sankyo, Biotronik, Portola, and Boehringer Ingelheim and has served as a speaker for Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, and Sanofi Aventis. Dr Larsen has been on the speaker bureaus for Bayer, BMS/Pfizer, Janssen Pharmaceuticals, Takeda, Roche Diagnostics, and Boehringer Ingelheim. The other authors report no conflicts.

References

1. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285:2864–2870.
2. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. 2010;137:263–272. doi: 10.1378/chest.09-1584.
3. Olesen JB, Lip GY, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *BMJ*. 2011;342:d124.
4. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. *Eur Heart J*. 2012;33:1500–1510. doi: 10.1093/eurheartj/ehr488.
5. Welles CC, Whooley MA, Na B, Ganz P, Schiller NB, Turakhia MP. The CHADS2 score predicts ischemic stroke in the absence of atrial fibrillation among subjects with coronary heart disease: data from the Heart and Soul Study. *Am Heart J*. 2011;162:555–561. doi: 10.1016/j.ahj.2011.05.023.
6. Mitchell LB, Southern DA, Galbraith D, Ghali WA, Knudtson M, Wilton SB; APPROACH investigators. Prediction of stroke or TIA in patients without atrial fibrillation using CHADS2 and CHA2DS2-VASc scores. *Heart*. 2014;100:1524–1530. doi: 10.1136/heartjnl-2013-305303.
7. Biancari F, Asim Mahar MA, Kangasniemi OP. CHADS2 and CHA2DS2-VASc scores for prediction of immediate and late stroke after coronary artery bypass graft surgery. *J Stroke Cerebrovasc Dis*. 2013;22:1304–1311. doi: 10.1016/j.jstrokecerebrovasdis.2012.11.004.
8. Hornero F, Martin E, Paredes F, Gil O, Cánovas S, García R, et al. Stroke after coronary artery bypass grafting: preoperative predictive accuracies of CHADS2 and CHA2DS2VASc stroke risk stratification schemes. *J Thorac Cardiovasc Surg*. 2012;144:1428–1435. doi: 10.1016/j.jtcvs.2012.07.053.
9. Poçi D, Hartford M, Karlsson T, Herlitz J, Edvardsson N, Caidahl K. Role of the CHADS2 score in acute coronary syndromes: risk of subsequent death or stroke in patients with and without atrial fibrillation. *Chest*. 2012;141:1431–1440. doi: 10.1378/chest.11-0435.
10. Lip GY, Lin HJ, Chien KL, Hsu HC, Su TC, Chen MF, et al. Comparative assessment of published atrial fibrillation stroke risk stratification schemes for predicting stroke, in a non-atrial fibrillation population: the Chin-Shan Community Cohort Study. *Int J Cardiol*. 2013;168:414–419. doi: 10.1016/j.ijcard.2012.09.148.
11. Hillen T, Coshall C, Tilling K, Rudd AG, McGovern R, Wolfe CD; South London Stroke Register. Cause of stroke recurrence is multifactorial: patterns, risk factors, and outcomes of stroke recurrence in the South London Stroke Register. *Stroke*. 2003;34:1457–1463. doi: 10.1161/01.STR.0000072985.24967.7F.
12. Dhamoon MS, Sciacca RR, Rundek T, Sacco RL, Elkind MS. Recurrent stroke and cardiac risks after first ischemic stroke: the Northern

Manhattan Study. *Neurology*. 2006;66:641–646. doi: 10.1212/01.wnl.0000201253.93811.f6.

13. Ntaios G, Lip GY, Makaritsis K, Papavasileiou V, Vemmou A, Koroboki E, et al. $CHADS_2$, $CHA_2S_2DS_2$-VASc, and long-term stroke outcome in patients without atrial fibrillation. *Neurology*. 2013;80:1009–1017. doi: 10.1212/WNL.0b013e318287281b.
14. CAPRIE Steering Commitee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet*. 1996;348:1329–1339.
15. Diener HC, Ringleb PA, Savi P. Clopidogrel for the secondary prevention of stroke. *Expert Opin Pharmacother*. 2005;6:755–764. doi: 10.1517/14656566.6.5.755.
16. Mainz J, Krog BR, Bjørnshave B, Bartels P. Nationwide continuous quality improvement using clinical indicators: the Danish National Indicator Project. *Int J Qual Health Care*. 2004;(16 suppl 1):i45–i50. doi: 10.1093/intqhc/mzh031.
17. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health*. 2011;39(7 suppl):30–33. doi: 10.1177/1403494811401482.
18. Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health*. 2011;39(7 suppl):38–41. doi: 10.1177/1403494810394717.
19. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health*. 2011;39(7 suppl):22–25. doi: 10.1177/1403494810387965.
20. Wildenschild C, Mehnert F, Thomsen RW, Iversen HK, Vestergaard K, Ingeman A, et al. Registration of acute stroke: validity in the Danish Stroke Registry and the Danish National Registry of Patients. *Clin Epidemiol*. 2014;6:27–36. doi: 10.2147/CLEP.S50449.
21. Wolbers M, Koller MT, Witteman JC, Steyerberg EW. Prognostic models with competing risks: methods and application to coronary risk prediction. *Epidemiology*. 2009;20:555–561. doi: 10.1097/EDE.0b013e3181a39056.
22. Olesen JB, Torp-Pedersen C. Stroke risk in atrial fibrillation: Do we anticoagulate $CHADS_2$ or CHA_2DS_2-VASc ≥1, or higher? *Thromb Haemost*. 2015;113:1165–1169.
23. Nielsen PB, Chao TF. The risks of risk scores for stroke risk assessment in atrial fibrillation. *Thromb Haemost*. 2015;113:1170–1173. doi: 10.1160/TH15-03-0210.
24. Weimar C, Diener HC, Alberts MJ, Steg PG, Bhatt DL, Wilson PW, et al; REduction of Atherothrombosis for Continued Health Registry Investigators. The Essen stroke risk score predicts recurrent cardiovascular events: a validation within the REduction of Atherothrombosis for Continued Health (REACH) registry. *Stroke*. 2009;40:350–354. doi: 10.1161/STROKEAHA.108.521419.

ONLINE SUPPLEMENT

Recurrent Stroke – The Value of the CHA_2DS_2VASc Score and the Essen Stroke Risk Score in a Nationwide Stroke Cohort

The online supplement contains:

Definitions of comorbidities
International Classification of Diseases (ICD)-8 and 10 codes and Anatomical Therapeutic Chemical (ATC) prescription codes applied for identification in the registries

Atrial fibrillation (AF) was determined as a diagnosis in the Danish National Patient Registry (ICD-8 and ICD-10 codes 42793, 42794, I48) or a diagnosis of AF in The Danish Stroke Registry.

Congestive heart failure was determined as the combination of a prior diagnosis of heart failure in The Danish National Patient Registry (ICD-8 and ICD-10 codes 42709, 42710, 42711, 42719, 42899, 78249, I110, I130, I132, I420, I50) and the prescription of a loop diuretic (C03C).

Hypertension was determined as a diagnosis of hypertension in The Danish National Patient Registry (ICD-8 and ICD-10 codes 400-404, 41009, 41109, 41209, 41309, 41409, 43000, 43001, 43008, 43009, 43100, 43101, 43108, 43109, 43200, 43201, 43202, 43208, 43209, 43309, 43409, 43509, 43600, 43601, 43609, 43700, 43701, 43708, 43709, 43809, I10-I15) therapy with at least two different classes of antihypertensive drugs, namely α adrenergic blockers (ATC-codes C02A, C02B, C02C), non-loop diuretics (ATC-codes C02DA, C02L, C03A, C03B, C03D, C03E, C03X, C07C, C07D, C08G, C09BA, C09DA, C09XA52), vasodilators (ATC-codes C02DB, C02DD, C02DG, C04, C05), β blockers (ATC-code C07), calcium channel blockers (ATC-codes C07F, C08, C09BB,C09DB), and renin-angiotensin system inhibitors (ATC-code C09) or a diagnosis of hypertension in The Danish Stroke Registry.

Diabetes mellitus was determined as a diagnosis of diabetes mellitus (ICD-8 and ICD-10 codes 24900, 24909, 25008, 25009, E100, E101, E109, E110, E111, E119) in The Danish National Patient Registry, the prescription of antidiabetics (ATC-code A10) or a diagnosis of diabetes mellitus in The Danish Stroke Registry.

Previous thromboembolism: In the CHA_2DS_2VASc score all patients were assigned two points for the index stroke.

Vascular disease (myocardial infarction, peripheral arterial disease and aortic plaque) was determined as a diagnosis in The Danish National Patient Registry (ICD-8 and ICD-10 codes 410, I21, I23, 440, 441, 442, 443, 444, 445, I702, I703, I704, I705, I706, I707, I708, I709, I71, I739, I700) or a diagnosis of previous myocardial infarction and/or peripheral arterial disease in The Danish Stroke Registry.

Previous myocardial infarction was determined as a diagnosis in The Danish National Patient Registry (ICD-8 and ICD-10 codes 410, I21, I23) or a diagnosis of previous myocardial infarction in The Danish Stroke Registry.

Other cardiovascular disease was determined as a diagnosis (ICD-10 codes I20, I22, I24, I25, I30-I39, I40-I47, I49, I50, I51, I52) or a procedure code (FNG/A/C/D/E) in The Danish National Patient Registry.

Peripheral arterial disease was determined as a diagnosis in The Danish National Patient Registry (ICD-8 and ICD-10 codes 440, 441, 442, 443, 444, 445, I702, I703, I704, I705, I706, I707, I708, I709, I71, I739) or a diagnosis of peripheral arterial disease in the DRS.

Smoking was determined as current or previous smoking according to The Danish Stroke Registry.

Additional transient ischemic attack (TIA) or ischemic stroke was determined a diagnosis of TIA in The Danish National Patient Registry (ICD-8 and ICD-10 codes 43509, 43599, G45) or a diagnosis of previous TIA in The Danish Stroke Registry. Patients with previous ischemic stroke were not included in the cohort.

Table I. Cox Proportional Hazard Analysis of Ratios of Stroke, Death, and Cardiovascular Event based on the Components of the CHA_2DS_2VASc Score and the Essen Stroke Risk Score

	1-year			5-year		
	Stroke	Death	Cardiovascular events	Stroke	Death	Cardiovascular events
CHF / LVD	1.10 (0.82-1.48)	2.95 (2.64-3.29)	1.40 (1.15-1.70)	1.28 (1.05-1.56)	2.90 (2.69-3.14)	1.55 (1.35-1.78)
Hypertension	1.22 (1.09-1.36)	1.22 (1.15-1.30)	1.28 (1.18-1.39)	1.26 (1.17-1.35)	1.23 (1.18-1.28)	1.31 (1.24-1.39)
Diabetes	1.33 (1.15-1.53)	1.24 (1.14-1.35)	1.44 (1.30-1.60)	1.34 (1.22-1.49)	1.35 (1.27-1.43)	1.45 (1.34-1.56)
Vascular disease	1.35 (1.17-1.56)	1.78 (1.66-1.93)	1.64 (1.48-1.81)	1.53 (1.39-1.68)	1.77 (1.68-1.86)	1.82 (1.70-1.95)
Sex (female)	0.87 (0.78-0.98)	1.30 (1.22-1.38)	0.91 (0.84-0.98)	0.88 (0.82-0.95)	1.21 (1.16-1.26)	0.87 (0.82-0.92)
Prev. TIA	1.19 (0.93-1.51)	0.97 (0.83-1.13)	1.50 (1.27-1.76)	1.38 (1.18-1.61)	1.00 (0.91-1.11)	1.46 (1.31-1.64)
PAD	1.43 (1.19-1.72)	1.77 (1.61-1.95)	1.72 (1.51-1.95)	1.51 (1.33-1.71)	1.87 (1.75-2.00)	1.75 (1.60-1.92)
Prev. MI	1.26 (1.00-1.58)	1.86 (1.67-2.08)	1.70 (1.47-1.97)	1.45 (1.26-1.69)	1.73 (1.60-1.87)	1.92 (1.74-2.13)
Other cardiovasc. dis.	1.24 (0.97-1.58)	1.21 (1.05-1.40)	1.53 (1.30-1.80)	1.49 (1.28-1.75)	1.13 (1.03-1.25)	1.84 (1.65-2.06)
Smoking	1.13 (1.01-1.26)	0.59 (0.56-0.63)	1.13 (1.04-1.22)	1.07 (0.99-1.15)	0.73 (0.70-0.76)	1.10 (1.04-1.16)
Age > 65 years	1.24 (1.11-1.39)	4.92 (4.50-5.44)	1.22 (1.12-1.33)	1.42 (1.31-1.54)	4.56 (4.29-4.85)	1.41 (1.33-1.50)
Age > 75 years	1.24 (1.11-1.38)	4.37 (4.08-4.68)	1.18 (1.08-1.28)	1.37 (1.27-1.48)	4.22 (4.04-4.41)	1.34 (1.27-1.42)

Data are hazard ratios (95% confidence intervals). Cardiovascular events represent the composite endpoint of stroke, transient ischemic attack, myocardial infarction or arterial thromboembolism. CHF indicates congestive heart failure; LVD, left ventricular dysfunction; TIA, transient ischemic attack; MI, myocardial infarction; CV, cardiovascular

Table II. Negative Predictive Values for the CHA_2DS_2VASc Score and the Essen Stroke Risk Score

Endpoint		CHA_2DS_2VASc Score	Essen Stroke Risk Score
Stroke	1-year	0.94 (0.94-0.95)	0.95 (0.94-0.96)
	5-year	0.84 (0.83-0.85)	0.88 (0.87-0.89)
Cardiovascular Events	1-year	0.93 (0.92-0.93)	0.94 (0.93-0.95)
	5-year	0.80 (0.79-0.81)	0.84 (0.82-0.86)

The negative predictive values are estimates of the proportion of patients with a score at or below the cut-off who remained event-free and alive during follow up. Cutoff values were 2 (CHA_2DS_2VASc) and 0 (Essen Stroke Risk Score). Cardiovascular events represent the composite endpoint of stroke, transient ischemic attack, myocardial infarction or arterial thromboembolism. CHA_2DS_2VASc indicates congestive heart failure, hypertension, age $\geq$ 75 years (2 points), diabetes mellitus, previous stroke or transient ischemic attack (2 points), vascular disease, age 65-74 years and sex class (female).

Table III. 1- and 5-year Incidence Rates of Stroke and Death Stratified by the CHA_2DS_2VASc Score and the Essen Stroke Risk Score in the Subgroup of Patients Treated with Antiplatelet Drugs and Statins.

	1-year rates						5-year rates					
	Stroke		Death		Cardiovascular Events		Stroke		Death		Cardiovascular Events	
CHA_2DS_2VASc Score	Events, n	Rate	Events, n	Rate	Events, n	Rate	Events, n	Rate	Events, n	Rate	Events, n	Rate
2	84	3.3	37	1.4	138	5.5	146	1.7	120	1.3	256	3.0
3	128	2.7	73	1.5	257	5.5	305	1.9	280	1.7	558	3.6
4	188	3.6	205	3.9	375	7.3	363	2.1	624	3.5	718	4.4
5	191	4.1	304	6.4	342	7.5	389	2.6	901	5.8	691	4.9
6	130	4.0	367	11.0	263	8.2	300	3.1	906	8.9	558	6.0
≥7	62	5.3	214	17.7	137	11.5	112	3.5	474	13.9	240	7.8
Essen Stroke Risk Score												
0	28	2.1	15	1.1	52	4.0	58	1.3	43	0.9	107	2.4
1	132	2.9	79	1.7	256	5.6	267	1.7	266	1.6	503	3.3
2	185	3.2	205	3.5	356	6.3	389	2.0	622	3.1	704	3.8
3	229	4.3	357	6.6	406	7.8	469	2.8	1040	5.9	826	5.2
4	131	4.3	291	9.4	263	8.9	277	3.1	762	8.0	535	6.2
≥5	75	4.6	253	15.1	179	11.2	155	3.5	572	12.2	346	8.2

Treatment with antiplatelet drugs (aspirin, clopidogrel and/or dipyridamole) and statins was defined as a claimed prescription of both drugs in the period from 90 days before until 90 days after the index event. Cardiovascular events represent the composite endpoint of stroke, transient ischemic attack, myocardial infarction or arterial thromboembolism. CHA_2DS_2VASc indicates congestive heart failure, hypertension, age ≥ 75 years (2 points), diabetes mellitus, previous stroke or transient ischemic attack (2 points), vascular disease, age 65-74 years and sex class (female).

Table IV. Cox Proportional Hazard Analysis Showing 1- and 5-year Hazard Ratios of Stroke, Death, and Cardiovascular Events Stratified by the CHA_2DS_2VASc Score and the Essen Stroke Risk Score in the Subgroup of Patients Treated with Antiplatelet Drugs and Statins.

	1-year hazard ratio			5-year hazard ratio		
CHA_2DS_2VASc Score	Stroke	Death	Cardiovascular Events	Stroke	Death	Cardiovascular Events
2	ref.	ref.	ref.	ref.	ref.	ref.
3	0.80 (0.60-1.05)	1.06 (0.71-1.57)	1.00 (0.81-1.23)	1.13 (0.93-1.38)	1.26 (1.02-1.56)	1.18 (1.02-1.37)
4	1.08 (0.83-1.39)	2.67 (1.88-3.79)	1.31 (1.08-1.60)	1.24 (1.03-1.51)	2.62 (2.15-3.18)	1.42 (1.23-1.63)
5	1.23 (0.95-1.59)	4.45 (3.16-6.26)	1.34 (1.10-1.64)	1.54 (1.27-1.86)	4.38 (3.62-5.29)	1.57 (1.36-1.81)
6	1.18 (0.90-1.55)	7.59 (5.41-10.65)	1.45 (1.19-1.79)	1.75 (1.44-2.13)	6.64 (5.49-12.68)	1.88 (1.62-2.18)
≥7	1.55 (1.11-2.15)	12.19 (8.60-17.28)	2.10 (1.65-2.66)	1.91 (1.49-2.45)	10.38 (8.49-12.68)	2.38 (1.99-2.83)
Essen Stroke Risk Score						
0	ref.	ref.	ref.	ref.	ref.	ref.
1	1.34 (0.89-2.01)	1.49 (0.86-2.59)	1.40 (1.04-1.88)	1.33 (1.00-1.77)	1.78 (1.29-2.46)	1.36 (1.11-1.68)
2	1.51 (1.01-2.24)	3.11 (1.84-5.25)	1.56 (1.17-2.09)	1.59 (1.20-2.09)	3.42 (2.51-4.66)	1.56 (1.28-1.92)
3	2.01 (1.36-2.97)	5.81 (3.47-9.75)	1.92 (1.44-2.57)	2.15 (1.64-2.83)	6.46 (4.76-8.77)	2.07 (1.70-2.54)
4	1.99 (1.33-3.00)	8.25 (4.91-13.87)	2.17 (1.61-2.92)	2.30 (1.73-3.05)	8.71 (6.40-11.84)	2.45 (1.99-3.01)
≥5	2.09 (1.36-3.23)	13.23 (7.86-22.28)	2.71 (1.99-3.69)	2.52 (1.86-3.41)	13.22 (9.69-18.02)	3.12 (2.51-3.87)

Treatment with antiplatelet drugs (aspirin, clopidogrel and/or dipyridamole) and statins was defined as a claimed prescription of both drugs in the period from 90 days before until 90 days after the index event. Data are hazard ratios (95% confidence intervals). Ref. indicates reference. Cardiovascular events represent the composite endpoint of stroke, transient ischemic attack, myocardial infarction or arterial thromboembolism. CHA_2DS_2VASc indicates congestive heart failure, hypertension, age ≥ 75 years (2 points), diabetes mellitus, previous stroke or transient ischemic attack (TIA) (2 points), vascular disease, age 65-74 years and sex class (female).

APPENDIX E. STUDY 2

White Matter Hyperintensities and Clinical Risk Scores in Recurrent Ischemic Stroke

Søren Due Andersen, MD[1,2]; Torben Bjerregaard Larsen, PhD[2,3]; Anders Gorst-Rasmussen, PhD[2,4]; Yousef Yavarian, MD[5]; Gregory Y. H. Lip, MD[2,6] & Flemming W. Bach, DMSc[1,7]

[1] Department of Neurology, Aalborg University Hospital, Aalborg, Denmark
[2] Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Faculty of Health, Aalborg University, Aalborg, Denmark
[3] Department of Cardiology, Center for Cardiovascular Research, Aalborg University Hospital, Denmark
[4] Unit of Clinical Biostatistics, Aalborg University Hospital, Aalborg, Denmark
[5] Department of Radiology, Aalborg University Hospital, Aalborg, Denmark
[6] University of Birmingham Institute of Cardiovascular Sciences, City Hospital, Birmingham, United Kingdom
[7] Department of Neurology, Aarhus University Hospital, Aarhus, Denmark

Cover title: Risk Scores in Recurrent Ischemic Stroke

Corresponding author:
Søren Due Andersen, MD
Department of Neurology, Aalborg University Hospital, Ladegaardsgade 5, 9000 Aalborg, Denmark
E-mail: s.due@rn.dk; phone: +45 97 66 22 00; fax +45 97 66 22 12

Key words
Ischemic stroke, Risk Stratification, White Matter Hyperintensities, Magnetic Resonance Imaging, Prognosis

Abstract

Background: Nearly one in five patients with ischemic stroke will experience a second stroke within five years. Stroke risk stratification schemes based solely on clinically variables perform only modest in non-atrial fibrillation (AF) patients and improvement of these schemes will enhance their clinical utility. Cerebral white matter hyperintensities are associated with an increased risk of incident ischemic stroke in the general population whereas the association with the risk of ischemic stroke recurrence is more ambiguous. In a non-AF stroke cohort we investigated the association between cerebral white matter hyperintensities and the risk of recurrent ischemic stroke, and we evaluated the predictive performance of the CHA_2DS_2VASc score and The Essen Stroke Risk Score (clinical scores) when augmented with information on white matter hyperintensities.

Methods: In a registry-based, observational cohort study, we included 832 patients (mean age 59.6 (SD 13.9) years; 42.0% females) with incident ischemic stroke and no AF. We assessed the severity of white matter hyperintensities on magnetic resonance imaging. Hazard ratios stratified by the white matter hyperintensities score and adjusted for the components of the CHA_2DS_2VASc score were calculated based on Cox proportional hazards analysis. Recalibrated clinical scores were calculated by adding one point to the score for the presence of white matter hyperintensities. The discriminatory performance of the clinical scores, the recalibrated scores, and the white matter hyperintensities score was assessed with the C-statistic.

Results: White matter hyperintensities were significantly associated with the risk of recurrent ischemic stroke after adjusting for clinical risk factors: The hazard ratios ranged from 1.65 (95% CI: 0.70-3.86) for mild changes to 5.28 (1.98-14.07) for the most severe changes. C-statistics for the prediction of recurrent ischemic stroke were 0.59 (0.51-0.65) for the CHA_2DS_2VASc score and 0.60 (0.53-0.68) for the Essen Stroke Risk Score. The recalibrated clinical scores showed improved C-statistics: the recalibrated CHA_2DS_2VASc score 0.62 (0.54-0.70) (p=0.024) and the recalibrated

Essen Stroke Risk Score 0.63 (0.56-0.71) (p=0.031). C-statistics of the white matter hyperintensities score were 0.62 (0.52-0.68) to 0.65 (0.58-0.73).

Conclusions: Increasing burden of white matter hyperintensities was independently associated with recurrent ischemic stroke in a cohort of non-AF ischemic stroke patients. Recalibration of the CHA_2DS_2VASc score and the Essen Stroke Risk Score with information on white matter hyperintensities led to improved discriminatory performance in ischemic stroke recurrence prediction. Risk scores based on white matter hyperintensities alone were at least as accurate as the established clinical risk scores in the prediction of ischemic stroke recurrence.

Introduction

In ischemic stroke patients, risk stratification score systems for the individual assessment of stroke recurrence risk are of great clinical relevance. The risk of stroke recurrence can be as high as 18% over a 5-year period [1,2], but varies considerably among patients. In patients with atrial fibrillation (AF) the CHA_2DS_2VASc (congestive heart failure, hypertension, age ≥ 75 years (2 points), diabetes mellitus, previous stroke or TIA (2 points), vascular disease, age 65-74 years and sex class (female)) score [3] has become widely used for the stratification of stroke and thromboembolic risk.

Stroke risk stratification in non-AF patients has been less intensively studied. Recently, we and others showed that the CHA_2DS_2VASc score and the Essen Stroke Risk Score (1 point for each of age 65-75 years, age above 75 years (2 points), hypertension, diabetes, myocardial infarction (MI), other cardiovascular disease (except MI and AF), peripheral arterial disease, smoking and previous stroke or TIA) perform only modestly for predicting the risk of recurrent ischemic stroke in non-AF patients [4,5]. Hence, it is of interest to consider alternative parameters that can improve upon these stroke risk stratification schemes.

Studies on cerebral white matter hyperintensities and the risk of recurrent stroke have shown varying results. Some studies found no association [7,8] whereas a number of newer studies have found an association between white matter hyperintensities and an increased risk of recurrent stroke [9–12], as well as a poorer prognosis after ischemic stroke [13–15]. Thus, the severity of white matter hyperintensities may hold important information to aid risk stratification for recurrent ischemic stroke.

In the present study, we used observational data from Danish patient registries to investigate whether the severity of white matter hyperintensities was associated with the risk of ischemic stroke recurrence, death, and cardiovascular events in a non-AF cohort of patients with incident ischemic stroke. Second, we investigated the predictive performance of the CHA_2DS_2VASc score and the Essen Stroke Risk Score when augmented with information on white matter hyperintensities.

Methods

Data Sources

The study was based on brain imaging studies from two Danish hospitals, The Danish Stroke Registry, and Danish national registries. The Danish Stroke Registry was established in 2003 and holds information on diagnosis and various clinical variables such as selected comorbidities, smoking habits and stroke severity on all Danish stroke patients [16]. Diagnoses in The Danish Stroke Registry rely on the best judgment of the treating physician based on the available information at the time of diagnosis (medical files, imaging, prescriptions, patients, or proxy self-report). The Danish National Patient Registry [17] has registered all hospital admissions in Denmark with corresponding discharge diagnoses since 1977. The National Prescription Registry [18] holds data on all prescriptions dispensed from Danish pharmacies since 1994, coded according to the Anatomic Therapeutic Chemical (ATC) Classification System. Lastly, The Danish Civil Registration System contains information on date of birth, sex, migration, and vital status of all citizens [19].

Study Population

The study population consisted of all patients aged 18 years or above, registered in The Danish Stroke Registry with an incident ischemic stroke (International Classification of Diseases 10th revision (ICD-10) codes I63 or I64) (index stroke), and referred to Aalborg University Hospital or Hjørring Hospital, Denmark in the period between January 1, 2005 and December 31, 2012. Only patients who had undergone a brain MRI scan within four weeks after the index stroke were included. Patients with a history of AF were excluded.

Data from the brain imaging studies and The Danish Stroke Registry were linked with information from The Danish National Patient Registry, The National Prescription Registry, and The Danish Civil Registration System via the unique personal identification number assigned to all Danish residents [19]. We calculated the CHA_2DS_2VASc score and the Essen Stroke Risk Score (clinical scores) based on the

information in the registries (as previously described in detail [4,20]). Antithrombotic treatment was defined as initiation or continuation of antithrombotics (aspirin, clopidogrel and/or dipyridamole) during the admission for the index stroke.

Neuroimaging

Brain imaging was performed on 1.5 or 3.0 Tesla magnetic resonance imaging (MRI) scanners. The choice of MRI scanner depended only on the availability of the scanners. Analysis of the images was performed by a neurologist blinded to patient characteristics. To quantify the interobserver agreement a random sample of 50 patients was also independently analyzed by a consultant neuroradiologist.

White matter hyperintensities were assessed on T2-weigted and/or T2 fluid-attenuated inversion recovery (FLAIR) images as hyperintense lesions, isointense on diffusion weighted images (DWI) [21]. The white matter hyperintensities were rated according to the Fazekas scale, and were categorized as deep white matter (DWMH) or periventricular (PVH) hyperintensities [22]. DWMH were rated as follows: 0=absence, 1=punctate foci, 2=beginning confluence of foci, 3=large confluent areas. PVH were rated as follows: 0=absence, 1="caps" or pencil-thin lining, 2=smooth "halo", 3=irregular PVH extending into the deep white matter. PVH extending > 1 cm into the adjacent white matter were considered to involve the deep white matter [23]. Hyperintensities in the deep grey nuclei and the brainstem were not rated. The total Fazekas score was calculated as the sum of DWMH and PVH, resulting in a score of 0-6. Acute ischemic infarcts were assessed as lesions hyperintense on DWI and hypointense on apparent diffusion coefficient (ADC) map. Lacunar infarction was defined as a round or ovoid DWI hyperintense lesion ≤ 20 mm situated in the cerebral hemispheric white matter, in the basal ganglia, or in the brain stem [24].

Outcomes

The primary outcomes were recurrent ischemic stroke, death, and cardiovascular events. Cardiovascular events were defined as the composite of ischemic stroke (ICD-10 codes I63, I64), TIA (ICD-10 code G45), myocardial infarction (ICD-10 codes I21, I23) or arterial thromboembolism (ICD-10 code I74). Diagnoses of

recurrent ischemic stroke were identified in The Danish Stroke Registry and all other diagnoses were identified in The Danish National Patient Registry. Patients were followed from the day of the index stroke and until the outcome event under study, death, emigration, or end of study (December 31, 2013), whichever came first.

Statistical Analysis

Continuous data were summarized as mean values and standard deviations and categorical data as counts and proportions. Event rates of recurrent stroke, death, and cardiovascular events were calculated and stratified by the DWMH score, the PVH score, the total Fazekas score, the CHA_2DS_2VASc score, and the Essen Stroke Risk Score. Unadjusted hazard ratios based on the Cox proportional hazard model were calculated for increasing values of the imaging scores and the clinical scores. In addition we calculated hazard ratios for increasing values of the neuroimaging scores adjusted for the components of the CHA_2DS_2VASc score. The reference was the lowest score on each scale: DWMH=0, PVH=1 (there were no patients with a score of 0), total Fazekas score=1, CHA_2DS_2VASc score=2 (since all patients were assigned two points for the index stroke), and Essen Stroke Risk Score=0. Due to the small size of the groups, patients with a CHA_2DS_2VASc score ≥ 6 were merged into a single stratum, and similarly patients with an Essen Stroke Risk Score ≥ 4 were merged into a single stratum.

We combined the neuroimaging scores and the clinical scores to recalibrated clinical scores by adding 1 point to the CHA_2DS_2VASc score and the Essen Stroke Risk Score for a DWMH score ≥ 2. We performed sensitivity analyses for the recalibrated scores by applying different cutoffs of the DWMH score and the total Fazekas score: DWMH score = 3, total Fazekas score ≥ 4, and total Fazekas score = 6. The discriminatory performance of the neuroimaging scores, the clinical scores, and the recalibrated scores was assessed with the C-statistic [25]. Predictive power of the scores were based on Somers' D rank statistic transformed to Harrell's C for survival models [26]. A two-sided P-value less than 0.05 was considered statistically

significant. Stata version 13 (Stata Corporation, College Station, TX) was used for statistical analysis.

Ethics

The study was approved by the Danish Data Protection Agency, file no. 2012-41-0633. In Denmark, no ethical approval is required for anonymous registry studies.

Results

In The Danish Stroke Registry, we identified 3,751 patients ≥ 18 years admitted to Aalborg University Hospital or Hjørring Hospital with incident ischemic stroke in the period between January 1, 2005 and December 31, 2012. We excluded 652 patients with a diagnosis of AF. In 2,267 patients there was no available brain MRI. Hence, the study cohort consisted of 832 patients with incident ischemic stroke, no AF, and an available brain MRI. The patients not included in the study due to no available MRI were older (mean age 70.9 versus 59.6 years), had more severe strokes (mean SSS score 44.7 versus 49.8) and higher CHA_2DS_2VASc score (mean score 4.4 versus 3.6).

In the rating of the random sample of 50 MRI scans we found full agreement between the two raters in 74% (DWMH) and 80% (PVH) of the cases. In the remaining there was a disagreement of maximally 1 point.

Baseline characteristics of the cohort are summarized in Table 1. Lacunar type infarct of the index stroke was found in 215 (25.9%) patients. During a mean follow-up time of 3.3 (SD 2.1) years, we observed 55 recurrent ischemic strokes, 80 deaths, and 102 cardiovascular events. During the first year of follow-up, the overall annual rates of recurrent ischemic stroke, death, and cardiovascular events were 3.4%, 4.1% and 7.4% respectively.

Incidence rates for the outcomes stratified by the neuroimaging scores and the clinical scores are shown in Figure 1 and in Table S-1 in the online supplementary material. Incidence rates for all outcomes increased with increasing values of the scores. Cox

proportional hazard ratios stratified by the neuroimaging scores, adjusted for the components of the CHA_2DS_2VASc score, are shown in Table 2. Increasing values of all scores were significantly associated with an increased rate of recurrent ischemic stroke. For the outcomes of death and cardiovascular events hazard ratios also showed an increasing trend. Unadjusted Cox hazard ratios stratified by the neuroimaging scores and the clinical scores are shown in Table S-2 in the online supplementary material.

Overall, the discriminatory performance of the scores was modest with C-statistics around 0.60-0.70 as shown in Table 3. When recalibrating the CHA_2DS_2VASc score and the Essen Stroke Risk Score by adding a point for a DWMH score ≥ 2, the discriminatory performance in terms of C-statistics was improved (Table 3). For the outcome of recurrent ischemic stroke these improvements were statistically significant (the recalibrated CHA_2DS_2VASc score versus the CHA_2DS_2VASc score: p=0.024; the recalibrated Essen Stroke Risk Score versus the Essen Stroke Risk Score: p=0.031). For the outcomes of death and cardiovascular events, the differences were not statistically significant.

The C-statistic for the prediction of ischemic stroke recurrence was numerically highest for the DWMH score and the total Fazekas score (around 0.65). These values were not significantly higher than those of the clinical scores (the DWMH score versus the CHA_2DS_2VASc score: p=0.13, versus the Essen Stroke Risk Score: p=0.25; the total Fazekas score versus the CHA_2DS_2VASc score: p=0.11, versus the Essen Stroke Risk Score: p=0.23). Neither was there any statistically significant differences between the C-statistics of the neuroimaging scores and the clinical scores for the outcomes death and cardiovascular events.

Sensitivity analyses

In the sensitivity analyses of the recalibrated scores with cutoffs of DWMH score = 3, total Fazekas score ≥ 4, and total Fazekas score = 6, the C-statistics for ischemic

stroke recurrence were comparable to the analyses with a cutoff of DWMH ≥ 2 (around 0.61) (data not shown). For the cutoff of the total Fazekas score ≥ 4, the C-statistics for ischemic stroke recurrence were significantly higher for the recalibrated scores compared to the original scores. For the cutoffs of DWMH = 3 and total Fazekas score = 6 the C-statistics of the recalibrated scores were not significantly different from those of the original scores.

Discussion

In the present study, our principal finding was that an increasing burden of white matter hyperintensities is associated with the risk of recurrent ischemic stroke in non-AF patients, even after adjusting for known stroke risk factors. Second, the combination of information on white matter hyperintensities with the CHA_2DS_2VASc score and the Essen Stroke Risk Score improved the discriminatory performance of these clinical scores.

This study confirms prior research showing that cerebral white matter hyperintensities are associated with an increased risk of recurrent stroke in ischemic stroke patients [9–12]. For the first time, we report that an increasing burden of periventricular and deep white matter hyperintensities, as well the total Fazekas score, are associated with an increasing risk of recurrent ischemic stroke after adjusting for known clinical stroke risk factors. This dose-response association has not been clearly demonstrated previously and it emphasizes that the burden of white matter hyperintensities holds important prognostic information. Previous studies indicate that the association between white matter hyperintensities and the clinical outcomes may be weaker among stroke patients with AF [10,12], hence, our finding may have been strengthened by the fact that the present study included only non-AF patients.

We have previously shown that the CHA_2DS_2VASc score and the Essen Stroke Risk Score by themselves perform only modestly in the prediction of ischemic stroke

recurrence in a nationwide non-AF ischemic stroke cohort [4]. The present study reveals a potential for improving these scores by adding information on white matter hyperintensities. Virtually all stroke patients undergo neuroimaging and therefore, these findings are valuable in the efforts to develop improved clinical risk stratification schemes based on readily accessible parameters.

Our findings are in contrast to the results of a recent study from the Athens Stroke Registry [12]. In this study, adding one point for leukoaraiosis on brain CT or MRI to the $CHADS_2$ (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, previous stroke or TIA (2 points)) and the CHA_2DS_2VASc score in AF and non-AF ischemic stroke patients did not increase the accuracy of these scores in stroke recurrence prediction. However, the discrepancies between the Greek study and our study may be explained by differences in the applied imaging modalities and the thresholds chosen to define the presence of white matter hyperintensities or leukoaraiosis. First, we included only patients who had undergone MRI, whereas in the Greek study, both CT and MRI were allowed. Second, as we have demonstrated, choosing cutoffs equal to moderate severity of the white matter hyperintensities (a DWMH score ≥ 2 and a total Fazekas score ≥ 4) resulted in an improved discriminatory performance of the recalibrated CHA_2DS_2VASc score and the recalibrated Essen Stroke Risk Score. On the other hand, choosing cutoffs that included only the most severe changes (a DWMH score = 3 and a total Fazekas score = 6) did not lead to a significantly improved predictive ability of the recalibrated clinical scores. In the Greek study, the definition of leukoaraiosis was probably reserved for relatively widespread changes and further, they applied a different neuroimaging rating scale.

We found that for the prediction of recurrent ischemic stroke, white matter hyperintensities burden alone performed on par with both the original clinical scores and the recalibrated clinical scores. Risk factors for white matter hyperintensities,

namely age and hypertension, and less well documented, diabetes [27], are comprised in the clinical scores. Thus, it can be argued that white matter hyperintensities are just an intermediate in the chain of cause and effect in the development of ischemic stroke [28]. However, the extent of white matter hyperintensities may indicate the individual cerebral susceptibly to these risk factors and therefore white matter hyperintensities may be a more disease specific marker for the risk of stroke recurrence among non-AF stroke patients. Consistent with this interpretation, the original clinical risk scores performed better than white matter hyperintensities for predicting death and cardiovascular events.

Strengths and limitations

The main strengths of our study are the relatively large size of the cohort, the completeness of the follow-up, and the application of MRI for the assessment of the cerebral changes. There are also several important limitations. First, since this was a register-based study, we cannot exclude misclassification of both the stroke diagnosis and comorbidities, although the validity of the stroke diagnosis in the Danish Stroke Registry has previously been shown to be high [29]. Second, we only included patients with an MRI scan. These patients were generally younger and healthier than patients without an MRI scan, and this selective inclusion may limit the generalizability of our findings. Third, MRI scans were rated by one neurologist only. Although a small validation sample was also rated by a consultant neuroradiologist and reproducibility was deemed acceptable, we cannot rule out rater bias.

In conclusion, increasing burden of white matter hyperintensities was independently associated with the risk of recurrent ischemic stroke after adjusting for risk factors within the CHA_2DS_2VASc score. Recalibration of the CHA_2DS_2VASc score and the Essen Stroke Risk Score with information on white matter hyperintensities led to improved discriminatory performance of these scores in ischemic stroke recurrence prediction. Risk scores based on white matter hyperintensities alone were at least as

accurate as established clinical risk scores in the prediction of recurrent ischemic stroke.

Disclosures

Dr. G.Y.H. Lip has served as a consultant for Bayer/Jensen, Merck, AstraZeneca, Sanofi, BMS/Pfizer and Boehringer Ingelheim, and has been on the speaker bureaus for Bayer, BMS/Pfizer, Boehringer Ingelheim, Roche and Sanofi. Dr. T.B. Larsen has served as an investigator for Janssen Scientific Affairs, LLC and Boehringer Ingelheim, and has been on the speaker bureaus for Bayer, BMS/Pfizer, Roche Diagnostics, Boehringer Ingelheim and Takeda Pharma.

Other researchers have nothing to declare.

References

1. Hillen T, Coshall C, Tilling K, Rudd AG, McGovern R, Wolfe CDA: Cause of stroke recurrence is multifactorial: patterns, risk factors, and outcomes of stroke recurrence in the South London Stroke Register. Stroke 2003 Jun;34:1457–63.

2. Dhamoon MS, Sciacca RR, Rundek T, Sacco RL, Elkind MS V: Recurrent stroke and cardiac risks after first ischemic stroke: the Northern Manhattan Study. Neurology 2006 Mar 14;66:641–6.

3. Lip GYH, Nieuwlaat R, Pisters R, Lane D a, Crijns HJGM: Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest 2010 Feb;137:263–72.

4. Andersen SD, Gorst-Rasmussen A, Lip GYH, Bach FW, Larsen TB: Recurrent Stroke: The Value of the CHA2DS2VASc Score and the Essen Stroke Risk Score in a Nationwide Stroke Cohort. Stroke 2015 Sep;46:2491–7.

5. Weimar C, Diener H-C, Alberts MJ, Steg PG, Bhatt DL, Wilson PWF, Mas J-L, Röther J: The Essen stroke risk score predicts recurrent cardiovascular events: a validation within the REduction of Atherothrombosis for Continued Health (REACH) registry. Stroke 2009 Feb;40:350–4.

6. Wardlaw JM, Smith C, Dichgans M: Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging. Lancet Neurol 2013 May;12:483–497.

7. Podgorska A, Hier DB, Pytlewski A, Czlonkowska A: Leukoaraiosis and stroke outcome. J Stroke Cerebrovasc Dis 2002 Jan;11:336–40.

8. Putaala J, Haapaniemi E, Kurkinen M, Salonen O, Kaste M, Tatlisumak T: Silent brain infarcts, leukoaraiosis, and long-term prognosis in young ischemic stroke patients. Neurology 2011 May 17;76:1742–9.

9. Melkas S, Sibolt G, Oksala NKJ, Putaala J, Pohjasvaara T, Kaste M, Karhunen PJ, Erkinjuntti T: Extensive white matter changes predict stroke recurrence up to 5 years after a first-ever ischemic stroke. Cerebrovasc Dis 2012 Jan;34:191–8.

10. Kim G-M, Park K-Y, Avery R, Helenius J, Rost N, Rosand J, Rosen B, Ay H: Extensive Leukoaraiosis Is Associated With High Early Risk of Recurrence After Ischemic Stroke. Stroke 2013 Dec 26;45:479–485.

11. Kumral E, Güllüoğlu H, Alakbarova N, Karaman B, Deveci EE, Bayramov A, Evyapan D, Gökçay F, Orman M: Association of Leukoaraiosis with Stroke Recurrence within 5 Years after Initial Stroke. J Stroke Cerebrovasc Dis 2015;24:573–582.

12. Ntaios G, Lip GYH, Lambrou D, Papavasileiou V, Manios E, Milionis H, Spengos K, Makaritsis K, Vemmos K: Leukoaraiosis and stroke recurrence risk in patients with and without atrial fibrillation. Neurology 2015 Mar 24;84:1213–9.

13. Arsava EM, Rahman R, Rosand J, Lu J, Smith EE, Rost NS, Singhal a B, Lev MH, Furie KL, Koroshetz WJ, Sorensen a G, Ay H: Severity of leukoaraiosis correlates with clinical outcome after ischemic stroke. Neurology 2009 Apr 21;72:1403–10.

14. Henninger N, Lin E, Baker SP, Wakhloo AK, Takhtani D, Moonis M: Leukoaraiosis predicts poor 90-day outcome after acute large cerebral artery occlusion. Cerebrovasc Dis 2012 Jan;33:525–31.

15. Kang H-J, Stewart R, Park M-S, Bae K-Y, Kim S-W, Kim J-M, Shin I-S, Cho K-H, Yoon J-S: White matter hyperintensities and functional outcomes at 2 weeks and 1 year after stroke. Cerebrovasc Dis 2013 Jan;35:138–45.

16. Mainz J, Krog BR, Bjørnshave B, Bartels P: Nationwide continuous quality improvement using clinical indicators: the Danish National Indicator Project. Int J Qual Health Care 2004 Apr;16 Suppl 1:i45–50.

17. Lynge E, Sandegaard JL, Rebolj M: The Danish National Patient Register. Scand J Public Health 2011;39:30–33.

18. Kildemoes HW, Sørensen HT, Hallas J: The Danish National Prescription Registry. Scand J Public Health 2011 Jul;39:38–41.

19. Pedersen CB: The Danish Civil Registration System. Scand J Public Health 2011;39:22–25.

20. Olesen JB, Lip GYH, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, Selmer C, Ahlehoff O, Olsen a.-MS, Gislason GH, Torp-Pedersen C: Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. Bmj 2011 Jan 31;342:d124–d124.

21. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, Lindley RI, O'Brien JT, Barkhof F, Benavente OR, Black SE, Brayne C, Breteler M, Chabriat H, DeCarli C, de Leeuw F-E, Doubal F, Duering M, Fox NC, Greenberg S, Hachinski V, Kilimann I, Mok V, Oostenbrugge R Van, Pantoni L, Speck O, Stephan BCM, Teipel S, Viswanathan A, Werring D, Chen C, Smith C, van Buchem M, Norrving B, Gorelick PB, Dichgans M: Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol 2013 Aug;12:822–838.

22. Fazekas F, Chawluk J, Alavi A, Hurtig H, Zimmerman R: MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. Am J Roentgenol 1987 Aug;149:351–356.

23. Fazekas F, Barkhof F, Wahlund LO, Pantoni L, Erkinjuntti T, Scheltens P, Schmidt R: CT and MRI rating of white matter lesions. Cerebrovasc Dis 2002 Jan;13 Suppl 2:31–6.

24. Potter GM, Marlborough FJ, Wardlaw JM: Wide variation in definition, detection, and description of lacunar lesions on imaging. Stroke 2011 Feb 1;42:359–66.

25. Pencina MJ, D'Agostino RB: Evaluating Discrimination of Risk Prediction Models. JAMA 2015 Sep 8;314:1063.

26. Newson R: Comparing the predictive powers of survival models using Harrell's C or Somers' D. Stata J 2010;339–358.

27. Pantoni L: Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol 2010 Jul;9:689–701.

28. Inzitari D: Leukoaraiosis: an independent risk factor for stroke? Stroke 2003 Aug;34:2067–71.

29. Wildenschild C, Mehnert F, Thomsen RW, Iversen HK, Vestergaard K, Ingeman A, Johnsen SP: Registration of acute stroke: validity in the Danish Stroke Registry and the Danish National Registry of Patients. Clin Epidemiol 2013 Jan;6:27–36.

Table 1. Baseline characteristics (n=832)

Demographics	
Age, years	59.6 (13.9)
Age > 65 years	307 (36.9)
Age > 75 years	120 (14.4)
Female sex	349 (42.0)
Risk factors	
Congestive heart failure	9 (1.1)
Hypertension	396 (47.6)
Diabetes	76 (9.1)
Previous TIA	46 (5.5)
Vascular disease	74 (8.9)
Previous myocardial infarction	21 (2.5)
Peripheral arterial disease	38 (4.6)
Other heart disease	32 (3.9)
Smoking (current or previous)	505 (60.7)
CHA_2DS_2VASc score	3.6 (1.3)
Essen Stroke Risk Score	1.9 (1.4)
Antithrombotic treatment	784 (94.3)
DWMH score	
0	311 (37.4)
1	292 (35.1)
2	150 (18.0)
3	79 (9.5)
PVH score	
0	0 (0.0)
1	525 (63.1)
2	192 (23.1)
3	115 (13.8)
Total Fazekas score	
0	0 (0.0)
1	307 (39.9)
2	211 (25.4)
3	94 (11.3)
4	106 (12.7)
5	36 (4.3)
6	78 (9.4)

Abbreviations: TIA = transient ischemic attack; CHA_2DS_2VASc = congestive heart failure, hypertension, age ≥ 75 years (2 points), diabetes mellitus, previous stroke or transient ischemic attack (2 points), vascular disease, age 65-74 years and sex class (female); DWMH: deep white matter hyperintensities; PVH: periventricular hyperintensities; DWI: diffusion weighted images.
Data are mean (SD) or n (%)

Table 2. Adjusted Cox proportional hazard analysis showing stratified hazard ratios of recurrent ischemic stroke, death, and cardiovascular events.

	Adjusted hazard ratio (95% CI)		
	Recurrent ischemic stroke	Death	Cardiovascular events
DWMH score			
0	1.00 (reference)	1.00 (reference)	1.00 (reference)
1	1.93 (0.89-4.18)	1.59 (0.80-3.16)	1.21 (0.72-2.03)
2	3.08 (1.35-7.02)	1.38 (0.64-3.00)	1.57 (0.88-2.83)
3	4.99 (1.88-13.22)	2.17 (0.97-4.89)	2.08 (1.02-4.24)
PVH score			
1	1.00 (reference)	1.00 (reference)	1.00 (reference)
2	2.00 (1.01-3.93)	1.79 (0.98-3.25)	1.37 (0.83-2.25)
3	3.40 (1.58-7.33)	2.06 (1.09-3.90)	1.83 (1.02-3.28)
Total Fazekas score			
1	1.00 (reference)	1.00 (reference)	1.00 (reference)
2	1.65 (0.70-3.86)	1.45 (0.66-3.17)	1.28 (0.73-2.24)
3	2.83 (1.10-7.27)	2.11 (0.92-4.82)	1.33 (0.65-2.69)
4	2.77 (1.12-6.88)	1.70 (0.72-3.99)	1.57 (0.81-3.02)
5	4.08 (1.32-13.52)	1.75 (0.58-5.25)	1.85 (0.74-4.66)
6	5.28 (1.98-14.07)	2.54 (1.10-5.83)	2.20 (1.07-4.53)

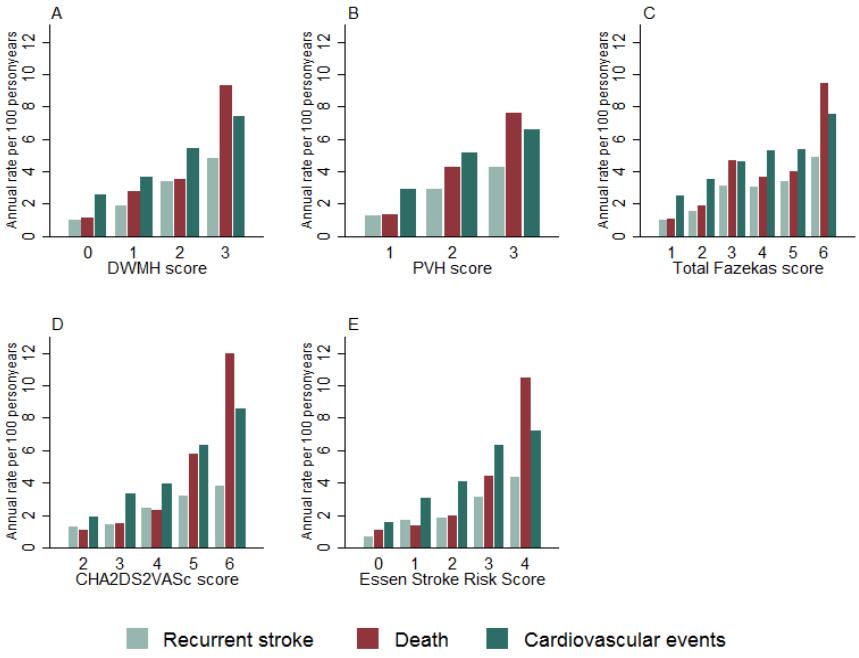
Analyses were adjusted for the components of the CHA_2DS_2VASc score. Cardiovascular events represent the composite endpoint of ischemic stroke, transient ischemic attack, myocardial infarction, or arterial thromboembolism. Abbreviations: DWMH = deep white matter hyperintensities; PVH = periventricular hyperintensities; CHA_2DS_2VASc = congestive heart failure, hypertension, age $\geq$ 75 years (2 points), diabetes mellitus, previous stroke or transient ischemic attack (2 points), vascular disease, age 65-74 years and sex class (female).

Table 3. C-statistics for the clinical scores, the combination of the clinical scores and a DWMH score ≥ 2, and the neuroimaging scores.

Score	Recurrent ischemic stroke	Death	Cardiovascular events
CHA_2DS_2VASc score	0.59 (0.51-0.65)	0.70 (0.64-0.77)	0.59 (0.54-0.65)
Essen Stroke Risk Score	0.60 (0.53-0.68)	0.69 (0.62-0.76)	0.60 (0.55-0.65)
CHA_2DS_2VASc score + DWMH score ≥2	0.62 (0.54-0.70)	0.72 (0.66-0.78)	0.61 (0.56-0.67)
Essen Stroke Risk Score + DWMH score ≥2	0.63 (0.56-0.71)	0.71 (0.65-0.77)	0.62 (0.57-0.67)
DWMH score	0.65 (0.58-0.73)	0.65 (0.66-0.78)	0.59 (0.54-0.65)
PVH score	0.62 (0.52-0.68)	0.66 (0.61-0.72)	0.58 (0.53-0.63)
Total Fazekas score	0.65 (0.58-0.73)	0.67 (0.61-0.73)	0.60 (0.54-0.65)

One point was added to the CHA_2DS_2VASc score and the Essen Stroke Risk Score for a DWMH score ≥2. Cardiovascular events represent the composite endpoint of ischemic stroke, transient ischemic attack, myocardial infarction, or arterial thromboembolism. Abbreviations: CHA_2DS_2VASc = congestive heart failure, hypertension, age ≥ 75 years (2 points), diabetes mellitus, previous stroke or transient ischemic attack (2 points), vascular disease, age 65-74 years and sex class (female); DWMH = deep white matter hyperintensity; PVH = periventricular hyperintensity. Data are C-statistics (95% CI).

Figure 1. Annual rates of recurrent ischemic stroke, death, and cardiovascular events per 100 person-years



The analyses were stratified by the DWMH score (A), the PVH score (B), the Total Fazekas score (C), the CHA_2DS_2VASc score (D), and the Essen Stroke Risk Score (E).
Cardiovascular events represent the composite endpoint of ischemic stroke, transient ischemic attack, myocardial infarction, or arterial thromboembolism. Abbreviations: DWMH = deep white matter hyperintensities; PVH = periventricular hyperintensities; CHA_2DS_2VASc = congestive heart failure, hypertension, age $\geq$ 75 years (2 points), diabetes mellitus, previous stroke or transient ischemic attack (2 points), vascular disease, age 65-74 years and sex class (female).

Supplementary Material

Table S-1. Event rates per 100 person-years according to levels of the risk scores.

	Recurrent ischemic stroke		Death		Cardiovascular events	
DWMH score						
0	11	1.0	13	1.1	28	2.6
1	18	1.9	28	2.8	34	3.7
2	16	3.4	18	3.5	25	5.4
3	10	4.8	21	9.3	15	7.4
PVH score						
0	0	0.0	0	0.0	0	0.0
1	24	1.3	26	1.4	52	2.9
2	17	2.9	27	4.3	29	5.1
3	14	4.3	27	7.6	21	6.6
Total Fazekas score						
1	11	1.0	12	1.0	27	2.5
2	11	1.6	14	1.9	24	3.5
3	9	3.1	15	4.7	13	4.6
4	10	3.0	13	3.7	17	5.3
5	4	3.4	5	4.0	6	5.3
6	10	4.9	21	9.4	15	7.5
CHA_2DS_2VASc score						
2	8	1.3	7	1.1	12	1.9
3	14	1.4	15	1.5	30	3.2
4	16	2.5	16	2.3	25	4.0
5	11	3.2	21	5.8	19	5.7
≥6	6	3.8	21	11.9	11	7.3
Essen Stroke Risk Score						
0	3	0.7	5	1.1	5	1.2
1	17	1.7	14	1.3	29	3.0
2	13	1.8	15	2.0	28	4.1
3	11	3.1	17	4.4	19	5.7
≥4	11	4.3	29	10.5	16	6.4

Cardiovascular events represent the composite endpoint of ischemic stroke, transient ischemic attack, myocardial infarction, or arterial thromboembolism. Abbreviations: DWMH = deep white matter hyperintensities; PVH = periventricular hyperintensities; CHA_2DS_2VASc = congestive heart failure, hypertension, age ≥ 75 years (2 points), diabetes mellitus, previous stroke or transient ischemic attack (2 points), vascular disease, age 65-74 years and sex class (female).

Table S-2. Unadjusted Cox proportional hazard analysis showing hazard ratios of recurrent ischemic stroke, death, and cardiovascular events.

	Hazard ratio (95% CI)		
	Recurrent ischemic stroke	Death	Cardiovascular events
DWMH score			
0	1.00 (reference)	1.00 (reference)	1.00 (reference)
1	1.86 (0.88-3.95)	2.42 (1.25-4.66)	1.39 (0.84-2.29)
2	3.33 (1.54-7.18)	3.08 (1.51-6.28)	2.02 (1.18-3.47)
3	4.48 (1.90-10.57)	7.77 (3.88-15.55)	2.56 (1.36-4.79)
PVH score			
1	1.00 (reference)	1.00 (reference)	1.00 (reference)
2	2.17 (1.16-4.04)	3.10 (1.81-5.31)	1.70 (1.08-2.68)
3	3.11 (1.61-6.02)	5.42 (3.16-9.30)	2.11 (1.27-3.51)
Total Fazekas score			
1	1.00 (reference)	1.00 (reference)	1.00 (reference)
2	1.53 (0.66-3.54)	1.77 (0.82-3.84)	1.37 (0.79-2.38)
3	3.00 (1.24-7.24)	4.42 (2.07-9.44)	1.77 (0.91-3.43)
4	2.95 (1.25-6.95)	3.43 (1.56-7.52)	2.02 (1.10-3.70)
5	3.39 (1.08-10.64)	3.78 (1.33-10.72)	2.08 (0.86-5.03)
6	4.50 (1.91-10.61)	8.45 (4.15-17.21)	2.67 (1.42-5.02)
CHA_2DS_2VASc			
2	1.00 (reference)	1.00 (reference)	1.00 (reference)
3	1.12 (0.47-2.68)	1.39 (0.57-3.41)	1.68 (0.87-3.28)
4	1.91 (0.82-4.45)	2.10 (0.87-5.12)	2.01 (1.01-4.00)
5	2.30 (0.92-5.73)	5.15 (2.18-12.12)	2.96 (1.46-6.02)
≥6	2.53 (0.87-7.32)	10.25 (4.34-24.20)	3.62 (1.65-7.97)
Essen Stroke Risk Score			
0	1.00 (reference)	1.00 (reference)	1.00 (reference)
1	2.48 (0.73-8.48)	1.20 (0.43-3.34)	2.65 (1.03-6.84)
2	2.56 (0.73-8.98)	1.77 (0.64-4.87)	3.42 (1.32-8.85)
3	4.17 (1.16-14.99)	3.76 (1.39-10.20)	4.83 (1.82-12.83)
≥4	5.50 (1.53-19.75)	8.64 (3.34-22.37)	5.27 (1.95-14.20)

The analyses were stratified by the neuroimaging and the clinical scores. Cardiovascular events represent the composite endpoint of ischemic stroke, transient ischemic attack, myocardial infarction, or arterial thromboembolism. Abbreviations: DWMH = deep white matter hyperintensities; PVH = periventricular hyperintensities.

APPENDIX F. STUDY 3

Original Paper

Cerebrovascular Diseases

Cerebrovasc Dis 2016;42:73–80
DOI: 10.1159/000445196

Received: December 10, 2015
Accepted: March 2, 2016
Published online: April 13, 2016

Multiple Silent Lacunes Are Associated with Recurrent Ischemic Stroke

Søren Due Andersen[a, b] Flemming Skjøth[a, c] Yousef Yavarian[d]
Flemming W. Bach[b, f] Gregory Y.H. Lip[a, g] Torben Bjerregaard Larsen[a, e]

[a]Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Faculty of Health, Aalborg University, [b]Department of Neurology, [c]Unit of Clinical Biostatistics and Bioinformatics, [d]Department of Radiology, and [e]Department of Cardiology, Center for Cardiovascular Research, Aalborg University Hospital, Aalborg, and [f]Department of Neurology, Aarhus University Hospital, Aarhus, Denmark; [g]Institute of Cardiovascular Sciences, University of Birmingham, City Hospital, Birmingham, UK

Key Words
Ischemic stroke · Lacunar stroke · Cerebral small vessel disease · MRI · Prognosis

Abstract
Background: Silent lacunes are a common finding on brain imaging in ischemic stroke patients, but the prognostic significance of these lesions is uncertain. We aimed at investigating the association of silent lacunes and the risk of ischemic stroke recurrence, death, and cardiovascular events in a cohort of patients with incident ischemic stroke and no atrial fibrillation (AF). ***Methods:*** We included 786 patients (mean age 59.5 (SD 14.0); 42.9% females) in a registry-based, observational cohort study on patients with first-ever ischemic stroke. On brain MRI we assessed the number of silent lacunes as none, single, or multiple and we calculated stratified incidence rates of the outcomes. Cox proportional hazard ratios (HRs) adjusted for age, gender, congestive heart failure, hypertension, diabetes, and vascular disease were calculated with no silent lacunes as reference. In additional analyses, we further adjusted for white matter hyperintensities. Patients were followed up until death or recurrence of ischemic stroke. ***Results:*** In 81 (10.3%) patients, a single silent lacune was present, and in 87 (11.1%) patients, multiple silent lacunes were present. Patients with at least one silent lacune were older (mean age 66.1 vs. 57.7, $p < 0.001$) and were more often hypertensive (60.1 vs. 43.4%, $p < 0.001$) compared to patients with no silent lacunes. During a median follow-up time of 2.9 (interquartile range 3.1) years, we observed 53 recurrent ischemic strokes, 76 deaths, and 96 cardiovascular events. Incidence rates per 100 person-years of ischemic stroke recurrence were 1.6, 2.5, and 5.0 for none, single, and multiple silent lacunes respectively. Corresponding incidence rates were 2.6, 2.4, and 4.4 for death, and 3.4, 4.0, and 6.6 for cardiovascular events respectively. Adjusted HRs of ischemic stroke recurrence were 1.53 (0.67–3.49) and 2.52 (1.25–5.09) for a single and multiple silent lacunes, respectively. Further adjustment for white matter hyperintensities maintained positive association although not significant. Corresponding adjusted HRs were 0.56 (0.25–1.25) and 0.65 (0.33–1.25) for death and 1.16 (0.61–2.22) and 1.51 (0.86–2.66) for cardiovascular events. ***Conclusions:*** In this large cohort of patients with incident ischemic stroke and no AF, an increasing number of silent lacunes was associated with increasing incidence rates of ischemic stroke recur-

E-Mail karger@karger.com
www.karger.com/ced

Torben Bjerregaard Larsen, MD, PhD
Department of Cardiology, Center for Cardiovascular Research
Aalborg University Hospital, Sdr. Skovvej 15
DK–9000 Aalborg (Denmark)
E-Mail tobl@rn.dk

rence. In the adjusted Cox proportional hazard analyses, the presence of multiple silent lacunes was significantly associated with an increased risk of ischemic stroke recurrence. The risk of death or cardiovascular events was not significantly influenced by the presence of silent lacunes.

Introduction

Lacunes are small fluid-filled cavities in the subcortical and deep regions of the brain, resulting from an ischemic infarct, or in rare cases a small hemorrhage [1]. Silent lacunes are similar lesions but without preceding corresponding clinical symptoms. Most knowledge on the prognostic significance of silent lacunes comes from studies on silent brain infarcts. There exists no universally accepted definition of silent brain infarcts, though most studies have included silent lacunes as well as cortical and territorial infarcts. In the Rotterdam Scan Study, lacunes constituted 95% of silent brain infarcts [2]; hence, the findings from studies on silent brain infarcts may largely apply to silent lacunes.

The prevalence of silent brain infarcts in population-based studies ranges from 8% [3] to 28% [4] and is strongly dependent on age [5]. In population-based cohorts in patients without symptomatic cerebrovascular disease, several studies have demonstrated silent brain infarcts to be a risk factor for future stroke [6–8].

In ischemic stroke patients, the prevalence of silent brain infarcts is also age dependent [9], but the prognostic significance is more ambiguous. Older studies did not find higher risk of mortality in stroke patients with silent brain infarcts, but these studies did not investigate the risk of stroke recurrence [9–11]. In a minor study of patients with lacunar stroke, silent lacunar infarcts increased the risk of stroke recurrence as well as the risk of mortality [12], and in a recent Finnish study of young stroke patients (15–49 years), the presence of multiple, but not a single, silent brain infarcts was associated with an increased risk of stroke recurrence but not with neither mortality nor a composite vascular endpoint [13]. In a subgroup analysis from the PRoFESS trial [14], a cohort of patients with non-cardioembolic ischemic stroke, silent brain infarcts were not significantly associated with neither recurrent stroke nor death [15]. Hence, the prognostic significance of silent brain infarcts in ischemic stroke patients is still debatable. Further, a majority of previous studies did not discriminate between the presence of a single or multiple silent brain infarcts. As shown in the study by Putaala et al. [13], the number of silent brain infarcts may carry important prognostic information. This information may be of value in future clinical stroke risk–stratification models.

In this study, we aimed at investigating the association of the number of silent lacunes with recurrent ischemic stroke, death, and cardiovascular events in a cohort of patients with incident ischemic stroke and no atrial fibrillation (AF). We hypothesized a stepwise positive correlation between the number of silent lacunes (categorized as none, single, or multiple) and stroke, death, and cardiovascular events.

Methods

Data Sources

We conducted a registry-based study on data from the Danish Stroke Registry, Danish national registries, and brain imaging studies from 2 Danish hospitals. The Danish Stroke Registry was founded in 2003, and it is mandatory for all Danish hospital departments treating stroke patients to report a standardized set of data to the registry. We have previously described the registry in details [16]. Diagnoses in the Danish Stroke Registry rely on the best judgment of the treating physician based on the available information at the time of diagnosis (medical files, imaging, prescriptions, patients, or proxy self-report). The sensitivity and the positive predictive value of a stroke diagnosis in the Danish Stroke Registry is ≥90% [17]. The Danish National Patient Registry [18] has registered all hospital admissions in Denmark with corresponding discharge diagnoses since 1977. Up to 1993, all diagnoses were coded according to the 8th revision of the International Classification of Diseases (ICD-8), and since 1994, all diagnoses are coded according to the ICD-10. The National Prescription Registry [19] keeps data on all prescriptions dispensed from Danish pharmacies since 1994, coded according to the Anatomic Therapeutic Chemical Classification System. The Danish Civil Registration System holds information on date of birth, gender, migration, and vital status of all citizens [20]. Information from the registries was linked using the unique personal registration number assigned to all Danish residents [20].

Study Population

The study population comprised all patients aged 18 years or above, registered in the Danish Stroke Registry with an incident ischemic stroke (ICD-10 codes I63 or I64; index stroke), and referred to Aalborg University Hospital or Hjørring Hospital, Denmark in the period between January 1, 2005 and December 31, 2012. We excluded patients with a history of AF, patients with a previous transient ischemic attack (TIA), and patients in whom no MRI had been performed within 6 weeks after the index stroke. See online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000445196) for the applied definitions of AF and TIA. Patients with previous TIA were excluded to assure that the observed silent lacunes were truly silent.

Comorbidity and Medication

Estimated glomerular filtration rate (eGFR) was calculated from a single creatinine measurement based on the Modification of Diet in Renal Disease-formula [21]. Antiplatelets comprised aspirin, clopidogrel, and dipyridamole and anticoagulants comprised warfarin, phenprocoumon, dabigatran, apixaban, and rivaroxaban. Antiplatelet use and anticoagulant use was defined as continuation or initiation of any of the defined drugs during the admission or a redeemed prescription of any of the defined drugs less than 30 days after the discharge. Statin use was defined as a redeemed prescription of any statin in the period from 90 days before until 30 days after the index stroke. For the applied definitions of congestive heart failure, hypertension, diabetes, vascular disease, and smoking refer to the online suppl. material.

Neuroimaging

Brain imaging was performed on 1.5 or 3.0 Tesla MRI scanners. A stroke neurologist blinded to patient characteristics performed brain imaging analysis. To quantify the reproducibility of the image analysis, we assessed a kappa value of interobserver agreement based on a random sample of 50 patients who were also independently analyzed by a consultant neuroradiologist.

Silent lacunes were considered round or ovoid well-defined areas of 3–15 mm in the territory of one perforating arteriole (hemispheric white matter, basal ganglia, brainstem or cerebellum) with signal characteristics similar to cerebrospinal fluid: hypointense on fluid-attenuated inversion recovery (FLAIR) and T1-weighted images and hyperintense on T2-weighted images [1]. In some patients, only T1-weighted or T2-weighted images were available. Lesions in the size ≤2 mm and with signal characteristics similar to lacunes were considered perivascular spaces [1]. The number of silent lacunes was classified as none, single, or multiple silent lacunes. White matter hyperintensities were assessed on T2-weighted and/or T2 FLAIR images as hyperintense lesions, isointense on diffusion weighted images (DWIs). The white matter hyperintensities were rated according to the Fazekas scale resulting in a score of 0–6 [22] and graded as none to mild (Fazekas score ≤2), moderate (Fazekas score 3–4) or severe (Fazekas score ≥5).

Acute ischemic infarcts were assessed as hyperintense lesions on DWI and hypointense on apparent diffusion coefficient map, and the location was classified as follows: anterior circulation (lesion(s) confined to one anterior circulation territory), posterior circulation, basal ganglia (lesion(s) confined to deep grey nuclei), >1 vascular territory, or no visible DWI lesion. Lacunar infarction was defined as a round or ovoid DWI hyperintense lesion ≤20 mm situated in the cerebral hemispheric white matter, in the basal ganglia, or in the brain stem [23].

Outcomes

The primary outcomes were recurrent ischemic stroke, death, and cardiovascular events. Recurrent ischemic stroke was identified in the Danish Stroke Registry as the first recurrence of ischemic stroke (ICD-10 codes I63, I64) after the index event. Cardiovascular events were defined as the composite of ischemic stroke, TIA (ICD-10 code G45), myocardial infarction (ICD-10 codes I21, I23) or arterial thromboembolism (ICD-10 code I74). Patients were followed from the day of the index stroke and until the outcome event under study, death, emigration, or end of study (December 31, 2013), whichever came first.

Statistical Analysis

Baseline continuous data were summarized using the mean and SD and categorical data by count and proportion. Continuous variables were compared with the Student's t test and categorical variables were compared with the Fisher's exact test. We calculated Goodman and Kruskal's gamma for the association between silent lacunes and white matter hyperintensities. Event rates per 100 person-years of recurrent ischemic stroke, death, and cardiovascular events were calculated for the whole cohort and stratified by the number of silent lacunes. Crude hazard ratios (HRs) based on the Cox proportional hazards model were calculated for an increasing number of silent lacunes with no silent lacunes as a reference. Adjusted HRs were adjusted for potential confounding effects of age, gender, congestive heart failure, hypertension, diabetes and vascular disease (model 1). In an additional model (model 2), we further adjusted for white matter hyperintensities. The effect of age was represented by a restricted cubic spline. The cumulative risk of recurrent stroke, death and cardiovascular events were calculated using the Kaplan–Meier estimator. Stata version 14 (Stata Corporation, College Station, Tex., USA) was used for the statistical analyses. A two-sided p value <0.05 was considered statistically significant.

Ethics

The study was approved by the Danish Data Protection Agency, file No. 2012-41-0633. In Denmark, no ethical approval is required for anonymous registry studies.

Results

In the Danish Stroke Registry, we identified 3,751 patients ≥18 years with incident ischemic stroke admitted to the 2 hospitals in the period between January 1, 2005 and December 31, 2012. We excluded 652 patients with AF and 135 patients with a previous TIA. In 2,178 patients, there was no available MRI scan from the acute phase of the index stroke; hence, 786 patients with incident ischemic stroke, no AF, and no previous TIA were included in the study cohort. The patients who did not undergo an MRI scan were older (mean age 70.9 vs. 59.5) and had more severe strokes (mean Scandinavian Stroke Scale (SSS) score 44.7 vs. 49.9) than the patients included in the study cohort.

The median time from hospital admission to MRI was 1.8 (interquartile range 2.5) days. Inter-rater agreement in the identification of silent lacunes in the sample of 50 MRI scans rated by 2 raters was found to be 98%, which equals a kappa value of 0.92.

Baseline characteristics of the study cohort are shown in table 1. In 168 (21.5%) patients, at least one silent lacune was present, and in 87 (11.1%) patients, multiple silent lacunes were found. The prevalence of silent lacunes increased markedly with increasing age as seen from

Table 1. Baseline characteristics (n = 786)

Demographics	
Age, years, mean (SD)	59.5 (14.0)
Female gender	337 (42.9)
Risk factors	
Congestive heart failure	9 (1.2)
Hypertension	369 (47.0)
Diabetes	73 (9.3)
Vascular disease	64 (8.14)
Smoking (current or previous)	468 (59.5)
Alcohol overuse	73 (9.29)
eGFR <45 ml/min/1.73 m^2	31 (3.9)
Medication	
Antiplatelets	754 (95.9)
Anticoagulants	28 (3.6)
Statins	433 (55.1)
Stroke severity	
SSS, mean (SD)	49.9 (11.4)
Mild, SSS score 43–58	648 (82.8)
Moderate, SSS score 26–42	96 (12.2)
Severe, SSS score ≤25	39 (5.0)
Lacunar type infarction	203 (25.8)
Number of silent lacunes	
0	618 (78.6)
1	81 (10.3)
≥2	87 (11.1)
White matter hyperintensities	
Mild	495 (63.0)
Moderate	185 (23.5)
Severe	106 (13.5)
Infarct location	
Anterior circulation	296 (37.7)
Posterior circulation	196 (24.9)
Basal ganglia	86 (10.9)
More than one vascular territory	75 (9.5)
Undetermined	133 (16.9)

Data are n (%) if not otherwise indicated. SSS = Scandinavian Stroke Scale.

Table 2. Baseline comparisons of patients with and without silent lacunes

	No silent lacunes (n = 618)	≥1 silent lacunes (n = 168)	p value
Age, years, mean (SD)	57.7 (13.7)	66.1 (12.9)	<0.001
Female gender	278 (45.0)	59 (35.1)	0.02
Congestive heart failure	4 (0.7)	5 (3.0)	0.03
Hypertension	268 (43.4)	101 (60.1)	<0.001
Diabetes	51 (8.3)	22 (13.1)	0.07
Vascular disease	52 (8.4)	12 (7.1)	0.75
Smoking (current or previous)	364 (58.9)	104 (61.9)	0.54
eGFR <45 ml/min/1.73 m^2	18 (2.9)	13 (7.7)	0.01
Moderate to severe stroke	107 (17.3)	28 (16.7)	0.91
Lacunar type infarction	143 (23.1)	60 (35.7)	0.001
Moderate to severe white matter hyperintensities	170 (27.5)	121 (72.0)	<0.001

Data are n (%) if not otherwise indicated.

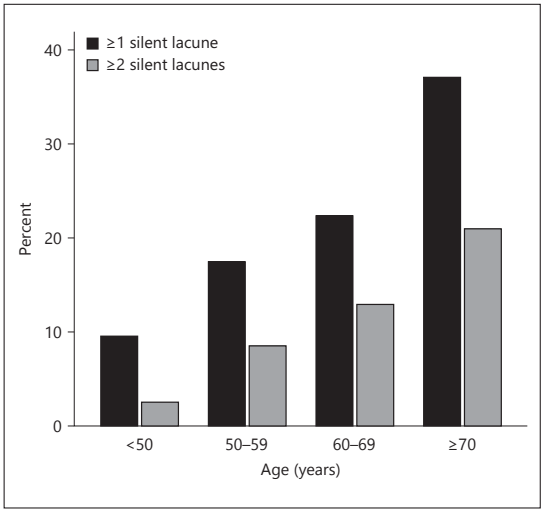


Fig. 1. Age-specific prevalence of ≥1 and ≥2 silent lacunes.

figure 1. Comparisons of patients with no silent lacunes and patients with at least one silent lacune are shown in table 2. Patients with at least one silent lacune were older, more often male and had a higher prevalence of congestive heart failure, hypertension, reduced renal function, and moderate to severe white matter hyperintensities. Goodman and Kruskal's gamma for the association between silent lacunes and white matter hyperintensities was 0.695. Lacunar infarction was more common among those with at least one silent lacune. There were no differences in stroke severity at presentation.

During a median follow-up time of 2.9 (interquartile range 3.1) years there were 53 recurrent ischemic strokes, 76 deaths, and 96 cardiovascular events (53 ischemic strokes, 29 TIAs, 12 myocardial infarctions, and 2 cases of arterial thromboembolism). No patients were lost to follow-up. We observed increasing rates of all the outcomes for an increasing number of silent lacunes (table 3), except for the outcome of death and the presence of a single silent lacune, where we found a slightly lower rate compared to no silent lacunes. The cumulative risks of the outcomes based on the Kaplan–Meier method are shown in figure 2. The crude HRs were increasing for an increasing number of silent lacunes as shown in table 3, again with the exception of the outcome of death and a single silent lacune. In the Cox proportional hazards analyses adjusted for stroke risk factors (model 1), the HRs for recurrent ischemic stroke and cardiovascular

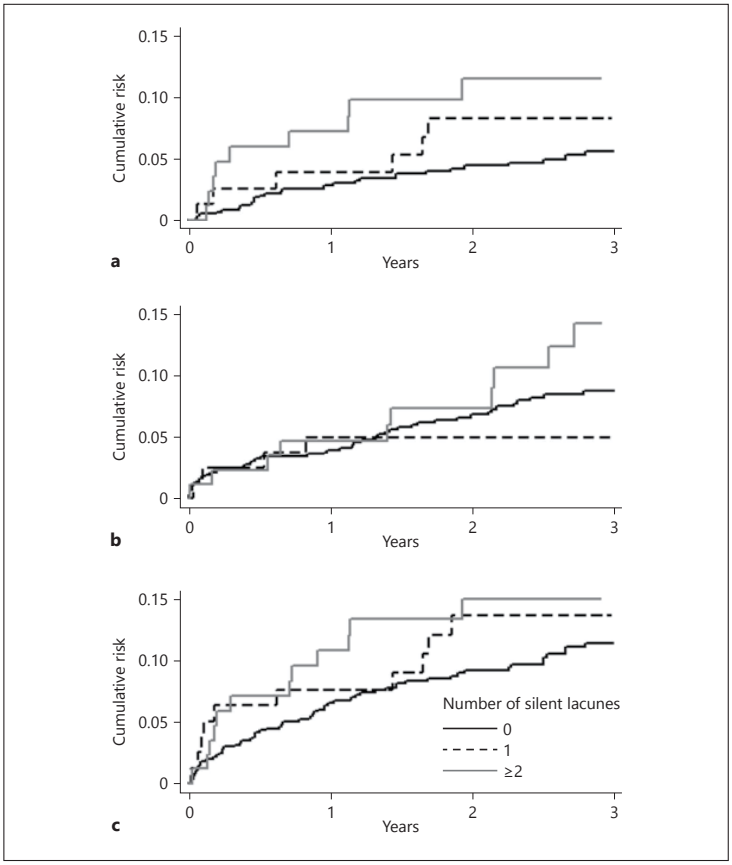


Fig. 2. Three-year cumulative risk of ischemic stroke recurrence (**a**), death (**b**), and cardiovascular events (**c**) stratified by the number of silent lacunes.

events were increasing for an increasing number of silent lacunes (table 3), but this was significant only for the outcome of recurrent stroke. The risk of death or cardiovascular events was not significantly influenced by the presence of silent lacunes. In the analyses additionally adjusted for white matter hyperintensities (model 2), we observed similar associations, though the positive association between recurrent ischemic stroke and silent lacunes was insignificant in this model.

Discussion

In the current study, we demonstrated that the presence of multiple silent lacunes was associated with an increased risk of recurrent ischemic stroke in a cohort of non-AF patients with incident ischemic stroke. Second, neither the presence of a single nor multiple silent lacunes was significantly associated with the risk of risk death or cardiovascular events.

A recent Finnish study investigated the prognostic significance of silent brain infarcts in young stroke patients [13]. They reported a significantly increased stroke recurrence risk in 15–49 years patients with multiple silent brain infarcts, without significant influence on either mortality or the composite vascular endpoint. Our results are in accordance with these findings, and we extended these results to comprise stroke patients of all ages, with the reservation that our analyses were confined to silent lacunes.

Lacunes are like white matter hyperintensities, a sign of cerebral small vessel disease [24]. Previous studies have documented that an increasing burden of white matter

Table 3. Rates per 100 person-years and Cox proportional hazard analysis of recurrent ischemic stroke, death, and cardiovascular events

Number of silent lacunes	Number	Rate	Crude HR (95% CI)	Model 1: adjusted HR (95% CI)[a]	Model 2: adjusted HR (95% CI)[b]
Recurrent ischemic stroke					
0	33	1.6	Reference	Reference	Reference
1	7	2.5	1.60 (0.71–3.62)	1.53 (0.67–3.49)	1.35 (0.58–3.11)
≥2	13	5.0	3.05 (1.61–5.81)	2.52 (1.25–5.09)	1.62 (0.74–3.55)
Death					
0	56	2.6	Reference	Reference	Reference
1	7	2.4	0.92 (0.42–2.03)	0.56 (0.25–1.25)	0.49 (0.22–1.10)
≥2	13	4.4	1.68 (0.92–3.07)	0.65 (0.33–1.25)	0.52 (0.26–1.03)
Cardiovascular events					
0	68	3.4	Reference	Reference	Reference
1	11	4.0	1.23 (0.65–2.32)	1.16 (0.61–2.22)	1.07 (0.55–2.06)
≥2	17	6.6	1.88 (1.11–3.21)	1.51 (0.86–2.66)	1.19 (0.64–2.23)

Cardiovascular events represent the composite endpoint of stroke, TIA, myocardial infarction, or arterial thromboembolism.

[a] Model 1: adjusted for age, sex, congestive heart failure, hypertension, diabetes, and vascular disease.

[b] Model 2: additionally adjusted for white matter hyperintensities.

hyperintensities is associated with an increased risk of stroke recurrence [25–27]. Since lacunes and white matter hyperintensities may be considered part of the same pathologic process, we are not surprised that increasing burdens of both these entities carry higher risk of stroke recurrence. We found that after further adjusting for white matter hyperintensities, the association between silent lacunes and recurrent ischemic stroke was still positive although weaker and no longer statistically significant. The weakening of the association was a result of the close correlation between silent lacunes and white matter hyperintensities. However, silent lacunes may still be a useful prognostic marker in models for stroke risk stratification.

In a recent study from Greece, it was shown that leukoaraiosis was associated with recurrent stroke in non-AF patients but not in patients with AF [28]. These findings suggest a potential difference in the prognostic significance of white matter hyperintensities in AF and non-AF related ischemic stroke. In the European Atrial Fibrillation Trial [29], which included patients with non-rheumatic AF and a recent TIA or non-disabling ischemic stroke, patients with a silent brain infarct on CT did not have a higher risk of recurrent stroke compared to patients with symptomatic infarcts. In our study we included only patients with no history of AF, and in the Finnish study by Putaala et al. [13] only 2.9% of the patients had AF at baseline. Thus, these findings indicate that there may exist differences in the prognostic significance of silent brain infarcts and silent lacunes in AF and non-AF patients, like in white matter hyperintensities. Future studies on prognosis of cerebral small vessel disease should take these considerations into account.

The HRs for cardiovascular events also increased with an increasing number of silent lacunes, although not statistically significant. In part, this was caused by the effect of recurrent strokes, which constituted more than half the number of the cardiovascular events. Surprisingly, the presence of silent lacunes resulted in non-significant adjusted HRs of death below 1.0. As expected, the adjustment for potential confounders resulted in lower estimates compared to the crude HRs, and we observed that the effect of the adjustment was essentially driven by age. However, it is possible that these estimates were biased due to the effect of one or several residual confounders.

We found that the prevalence of silent lacunes strongly depended on age. This is in agreement with older studies on silent brain infarcts in stroke patients [9], and with population-based studies [2]. Though it seems that silent lacunes, in part, could be a phenomenon of normal ageing, our age-adjusted analyses showed that multiple silent lacunes were associated with a 2.5-fold higher risk of recurrent ischemic stroke. Therefore, the finding of silent lacunes on brain imaging in stroke patients should be

considered an ominous sign, and should be considered in the prognostication and the counseling of the patient. Also, attention should be paid the potential cognitive consequences of silent lacunes. Neuropsychological disturbances are common in patients with silent lacunes but may easily go unrecognized [30]. At present, no evidence exists that ischemic stroke patients with silent lacunes should be treated differently.

The main strengths of our study are the relatively large size of the cohort, the completeness of the follow-up, and the application of MRI for the assessment of silent lacunes. There are also important limitations to consider. First, we did a registry-based study; thus, we cannot rule out misclassification of both the diagnosis of stroke and the comorbidities, but the validity of the Danish Stroke Registry is high. Second, we included only those patients who had done an MRI scan. Compared to the entire stroke cohort, these patients were younger and had minor strokes, and this selection may be a potential limitation to the generalizability of our findings. Third, MRI scans were rated only by a single stroke neurologist. Although a small validation sample was also rated by a consultant neuroradiologist and reproducibility was very high, we cannot rule out rater bias.

In conclusion, multiple silent lacunes are associated with an increased risk of ischemic stroke recurrence in patients with incident ischemic stroke and no AF. The risk of death or cardiovascular events was not significantly influenced by the presence of silent lacunes.

Disclosure Statement

Dr. G.Y.H. Lip has served as a consultant for Bayer/Jensen, Merck, AstraZeneca, Sanofi, BMS/Pfizer and Boehringer Ingelheim, and has been on the speaker bureaus for Bayer, BMS/Pfizer, Boehringer Ingelheim, Roche and Sanofi. Dr. T.B. Larsen has served as an investigator for Janssen Scientific Affairs, LLC and Boehringer Ingelheim, and has been on the speaker bureaus for Bayer, BMS/Pfizer, Roche Diagnostics, Boehringer Ingelheim and Takeda Pharma.

Other researchers have nothing to declare.

References

1 Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, Lindley RI, O'Brien JT, Barkhof F, Benavente OR, Black SE, Brayne C, Breteler M, Chabriat H, DeCarli C, de Leeuw FE, Doubal F, Duering M, Fox NC, Greenberg S, Hachinski V, Kilimann I, Mok V, Oostenbrugge RV, Pantoni L, Speck O, Stephan BC, Teipel S, Viswanathan A, Werring D, Chen C, Smith C, van Buchem M, Norrving B, Gorelick PB, Dichgans M: Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol 2013;12:822–838.

2 Vermeer SE, Koudstaal PJ, Oudkerk M, Hofman A, Breteler MM: Prevalence and risk factors of silent brain infarcts in the population-based Rotterdam scan study. Stroke 2002;33:21–25.

3 Schmidt R, Schmidt H, Pichler M, Enzinger C, Petrovic K, Niederkorn K, Horner S, Ropele S, Watzinger N, Schumacher M, Berghold A, Kostner GM, Fazekas F: C-reactive protein, carotid atherosclerosis, and cerebral small-vessel disease: results of the Austrian stroke prevention study. Stroke 2006;37:2910–2916.

4 Price TR, Manolio TA, Kronmal RA, Kittner SJ, Yue NC, Robbins J, Anton-Culver H, O'Leary DH: Silent brain infarction on magnetic resonance imaging and neurological abnormalities in community-dwelling older adults. The cardiovascular health study. CHS collaborative research group. Stroke 1997;28:1158–1164.

5 Vermeer SE, Longstreth WT Jr, Koudstaal PJ: Silent brain infarcts: a systematic review. Lancet Neurol 2007;6:611–619.

6 Bernick C, Kuller L, Dulberg C, Longstreth WT Jr, Manolio T, Beauchamp N, Price T: Silent MRI infarcts and the risk of future stroke: the cardiovascular health study. Neurology 2001;57:1222–1229.

7 Vermeer SE, Hollander M, van Dijk EJ, Hofman A, Koudstaal PJ, Breteler MM: Silent brain infarcts and white matter lesions increase stroke risk in the general population: the Rotterdam scan study. Stroke 2003;34:1126–1129.

8 Bokura H, Kobayashi S, Yamaguchi S, Iijima K, Nagai A, Toyoda G, Oguro H, Takahashi K: Silent brain infarction and subcortical white matter lesions increase the risk of stroke and mortality: a prospective cohort study. J Stroke Cerebrovasc Dis 2006;15:57–63.

9 Jørgensen HS, Nakayama H, Raaschou HO, Gam J, Olsen TS: Silent infarction in acute stroke patients. Prevalence, localization, risk factors, and clinical significance: the Copenhagen stroke study. Stroke 1994;25:97–104.

10 Boon A, Lodder J, Heuts-van Raak L, Kessels F: Silent brain infarcts in 755 consecutive patients with a first-ever supratentorial ischemic stroke. Relationship with index-stroke subtype, vascular risk factors, and mortality. Stroke 1994;25:2384–2390.

11 Brainin M, McShane LM, Steiner M, Dachenhausen A, Seiser A: Silent brain infarcts and transient ischemic attacks. A three-year study of first-ever ischemic stroke patients: the Klosterneuburg stroke data bank. Stroke 1995;26:1348–1352.

12 de Jong G, Kessels F, Lodder J: Two types of lacunar infarcts: further arguments from a study on prognosis. Stroke 2002;33:2072–2076.

13 Putaala J, Haapaniemi E, Kurkinen M, Salonen O, Kaste M, Tatlisumak T: Silent brain infarcts, leukoaraiosis, and long-term prognosis in young ischemic stroke patients. Neurology 2011;76:1742–1749.

14 Diener HC, Sacco R, Yusuf S: Rationale, design and baseline data of a randomized, double-blind, controlled trial comparing two antithrombotic regimens (a fixed-dose combination of extended-release dipyridamole plus ASA with clopidogrel) and telmisartan versus placebo in patients with strokes: the prevention regimen for effectively avoiding second strokes trial (PRoFESS). Cerebrovasc Dis 2007;23:368–380.

15 Weber R, Weimar C, Wanke I, Möller-Hartmann C, Gizewski ER, Blatchford J, Hermansson K, Demchuk AM, Forsting M, Sacco RL, Saver JL, Warach S, Diener HC, Diehl A: Risk of recurrent stroke in patients with silent brain infarction in the prevention regimen for effectively avoiding second strokes (PRoFESS) imaging substudy. Stroke 2012;43:350–355.

16 Andersen SD, Gorst-Rasmussen A, Lip GY, Bach FW, Larsen TB: Recurrent stroke: the value of the CHA2DS2VASc score and the Essen stroke risk score in a nationwide stroke cohort. Stroke 2015;46:2491–2497.

17 Wildenschild C, Mehnert F, Thomsen RW, Iversen HK, Vestergaard K, Ingeman A, Johnsen SP: Registration of acute stroke: validity in the Danish stroke registry and the Danish national registry of patients. Clin Epidemiol 2013;6:27–36.
18 Lynge E, Sandegaard JL, Rebolj M: The Danish national patient register. Scand J Public Health 2011;39(7 suppl):30–33.
19 Kildemoes HW, Sørensen HT, Hallas J: The Danish national prescription registry. Scand J Public Health 2011;39(7 suppl):38–41.
20 Pedersen CB: The Danish civil registration system. Scand J Public Health 2011;39(7 suppl):22–25.
21 Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F: Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006;145:247–254.
22 Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA: MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. AJR Am J Roentgenol 1987;149:351–356.
23 Potter GM, Marlborough FJ, Wardlaw JM: Wide variation in definition, detection, and description of lacunar lesions on imaging. Stroke 2011;42:359–366.
24 Pantoni L: Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol 2010;9:689–701.
25 Melkas S, Sibolt G, Oksala NK, Putaala J, Pohjasvaara T, Kaste M, Karhunen PJ, Erkinjuntti T: Extensive white matter changes predict stroke recurrence up to 5 years after a first-ever ischemic stroke. Cerebrovasc Dis 2012;34:191–198.
26 Kim GM, Park KY, Avery R, Helenius J, Rost N, Rosand J, Rosen B, Ay H: Extensive leukoaraiosis is associated with high early risk of recurrence after ischemic stroke. Stroke 2014;45:479–485.
27 Kumral E, Güllüoğlu H, Alakbarova N, Karaman B, Deveci EE, Bayramov A, Evyapan D, Gökçay F, Orman M: Association of leukoaraiosis with stroke recurrence within 5 years after initial stroke. J Stroke Cerebrovasc Dis 2015;24:573–582.
28 Ntaios G, Lip GY, Lambrou D, Papavasileiou V, Manios E, Milionis H, Spengos K, Makaritsis K, Vemmos K: Leukoaraiosis and stroke recurrence risk in patients with and without atrial fibrillation. Neurology 2015;84:1213–1219.
29 Silent brain infarction in nonrheumatic atrial fibrillation. EAFT study group. European atrial fibrillation trial. Neurology 1996;46:159–165.
30 Grau-Olivares M, Arboix A: Mild cognitive impairment in stroke patients with ischemic cerebral small-vessel disease: a forerunner of vascular dementia? Expert Rev Neurother 2009;9:1201–1217.

ISSN (online): 2246-1302
ISBN (online): 978-87-7112-700-3

AALBORG UNIVERSITY PRESS