Health economic aspects of stroke

Stroke prevention and effects on spouses' healthcare consumption and income

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This too shall pass
- Edward Fitzgerald

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ABSTRACT

The overall aim of this thesis was to investigate two health economic aspects of stroke: (i) the clinical and cost-effectiveness of stroke prevention with left atrial appendage occlusion (LAAO) among persons with atrial fibrillation (AF) and contraindication to OAC, (ii) the long-term consequences of stroke on spouses' healthcare utilisation and financial situation and its potential impact in health economic evaluations.

The long-term clinical effectiveness and cost-effectiveness of LAAO among persons with AF and contraindications to OAC were estimated using a systematic review, meta-analysis, and a decision-analytic model. These studies show that LAAO is clinically effective and cost-effective. Further, spouses of persons with stroke healthcare utilisation and financial situation were investigated using a difference-in-differences approach. A significant increase in the number of days with inpatient care was identified among spouses. No statistically significant differences were seen among the overall population of spouses' financial situation. However, younger female spouses' income from paid work significantly decreased.

In conclusion, LAAO is clinically and cost-effective in a subpopulation of persons with AF that currently can be recommended LAAO in Europe. Further, there is a limited impact on healthcare utilisation and financial consequences in the overall population of spouses of persons with stroke.

Keywords: healthcare utilisation, income, informal care, left atrial appendage occlusion, spouse, stroke prevention

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SAMMANFATTNING PÅ SVENSKA

Stroke är en av de sjukdomar som bidrar med mest dödlighet globalt. Stroke har i många fall ett akut förlopp och påverkar inte bara den person som får en stroke utan även anhörigas vardag kan påverkas. Vidare är stroke en kostsam sjukdom och i Sverige, och 2009 uppgavs kostnaden relaterad till stroke vara ca 5 miljarder svenska kronor.

Det övergripande syftet med denna avhandling är att undersöka två hälsoekonomiska aspekter av stroke. Dels att undersöka den strokeförebyggande effekten samt kostnadseffektiviteten av stängning av vänster förmaksöra (LAAO) bland patienter med förmaksflimmer (FF), förhöjd risk för ischemisk stroke och kontraindikation för antikoagulantia. Vidare, syftar denna avhandling till att analysera hälso-och sjukvårdsutnyttjande samt ekonomiska situation bland partners till personer med stroke och den potentiella betydelsen av att inkludera dessa konsekvenser i hälsoekonomiska utvärderingar.

Avhandlingen består av fyra studier. Studie I är en systematisk översikt och metaanalys som undersöker den stroke förebyggande effekten av LAAO bland personer med FF, förhöjd risk för ischemisk stroke och kontraindikation för antikoagulantia. Studien visar att LAAO kan vara effektivt för att förebygga stroke i denna population. Studie II, undersöker kostnadseffektiviteten av LAAO jämför med ingen antitrombotisk behandling för samma population som i studie I, och kostnadseffektiviteten undersöks via en modellanalys. Studien visar att LAAO är kostnadseffektivt jämfört med ingen antitrombotisk behandling. Studie III och IV, estimerar långtidseffekterna på hälso-och sjukvårdsutnyttjande (studie III) och ekonomisk situation (studie IV) av att vara partner till en person med förstagångsstroke, och för att analysera data användes en difference-in-differences metod. Studie III, visar att partners till personer med förstagångsstroke har statistiskt signifikant fler dagar med slutenvård, medan besöken i primärvård och öppen specialistvård minskar (icke statistiskt signifikant). I studie IV identifieras ingen statistisk signifikant skillnad gällande partnerns individuella ekonomiska situation. Men i en subgruppsanalys, identifieras en statistiskt signifikant minskad individuell inkomst från arbete bland partners som är yngre kvinnor.

Sammantaget visar studie I och II, att LAAO är effektivt för att förebygga stroke samt kostnadseffektivt i den aktuella populationen. Slutsatsen från studie III och IV, är att effekten på partners till personer med stroke hälso-och sjukvårdutnyttjande och ekonomisk situation är begränsad.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Labori, F., Bonander, C., Persson, J., & Svensson, M. Clinical follow-up of left atrial appendage occlusion in patients with atrial fibrillation ineligible of oral anticoagulation treatment- a systematic review and meta-analysis.

Journal of Interventional Cardiac Electrophysiology, 2021, 2:215-225

II. Labori, F., Persson, J., Bonander, C., Jood, K., & Svensson, M. Cost-effectiveness analysis of left atrial appendage occlusion in patients with atrial fibrillation and contraindication to oral anticoagulation.

European Heart Journal, 2021, 31;43(13): 1348-1356.

III. Labori, F., Bonander, C., Svensson, M., & Persson, J. Long-term effects on healthcare utilisation among spouses of persons with stroke.

Submitted manuscript

IV. Labori, F., Persson, J., Svensson, M., & Bonander, C. The impact of stroke on spousal and family income: longitudinal evidence from Swedish national registries.

Manuscript

CONTENT

ABBREVIATIONS

AF	Atrial Fibrillation
APT	Antiplatelet treatment
Chi2	Chi-square test
CI	Confidence Interval
COMPARE	COMPARing Effectiveness and safety of Left Atrial Appendage Occlusion to standard of care for atrial fibrillation patients at high stroke risk and ineligible to use oral anticoagulation therapy
CVD	Cardiovascular disease
DAPT	Dual antiplatelet treatment
DMC	The Danish Medicine Council
DSA	Deterministic sensitivity analysis
EEA	European Economic Area
EQ-5D-3L	EuroQol 5 Dimensions 3 Levels
ESC	European Society of Cardiology
EU	European Union
EUR	Euro
GDP	Gross Domestic Product
HRQoL	Health-Related Quality of Life
ICER	Incremental Cost-Effectiveness Ratio
IoT	Income and Tax register
LAA	Left Atrial Appendage

LAAO	Left Atrial Appendage Occlusion
LISA	Longitudinal Integrated Database for Health Insurance and Labour Market Studies
mRS	modifed Rankin Scale
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NOAC	Non-vitamin-K antagonist oral anticoagulant
NOMA	The Norwegian Medicine Agency
OAC	Oral anticoagulation
PGM	Proxy Good Method
PREVAIL	Prospective Randomized Evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy
PICO	Patient, Intervention, Control, Outcome
PRISMA	The Preferred Reporting Items for Systematic reviews and Meta-Analyses
PROTECT-AF	Watchman Left atrial Appendage Closure Technology for Embolic Protection in Patients With Atrial Fibrillation
PSA	Probabilistic Sensitivity Analysis
QALY	Quality-adjusted Life-Year
RAMS	Labour market registry
RCT	Randomised Controlled Trial
RTB	Register of the total population

SEK	Swedish krona
SF-36	36-items short-form health survey
TIA	Transient Ischemic Attack
TLV	The Dental and Pharmaceutical Benefits Agency
UREG	Education of the population register
VKA	Vitamin-K antagonist
WTP	Willingness To Pay

1 INTRODUCTION

The general concept of health economics is that there are limited resources and an unlimited demand for health in society. Over the last decade, the percentage of the gross domestic product (GDP) spent on healthcare has increased in the majority of countries in the European Union (EU) and the European Economic Area (EEA). In Sweden, the share of GDP spent on healthcare was approximately 11% in 2019.[1] With the increased expenditure on health, the healthcare sector also has larger opportunities to prevent and treat illness. However, simultaneously the development of new and often expensive treatment alternatives is made available, which makes it important to consider the clinical and cost-effectiveness of interventions. To prevent health expenditures from reaching unreasonable levels, decision-makers must prioritise between treatments and how the limited resources should be allocated.

Stroke is one of the diseases that causes the most disability and deaths worldwide.[2] The stroke event occurs with little warning and can affect the patients' and their relatives' daily life. In addition to the disability and mortality related to the disease, stroke is costly for society. In 2015, a cost of 45 billion Euro (EUR) was connected to stroke in the EU, where approximately half of the cost was direct healthcare costs.[3] Further, 16 billion EUR (35%) was related to the informal care of persons with stroke[3]. In Sweden, the cost was estimated to be around 500 million EUR; however, this estimate does not include the cost of informal care.[4]

Stroke is a disease that, to a certain extent, is preventable, and thereby the disability, mortality and costs related to stroke can be lowered. Risk factors of stroke that can be modified through primary prevention are high blood pressure, high cholesterol, smoking and atrial fibrillation (AF).[5] There is an increasing number of patients receiving percutaneous Left Atrial Appendage Occlusion (LAAO) as stroke preventive treatment, which is a relatively expensive treatment. However, little is known about the stroke preventive effect as well as the cost-effectiveness of LAAO in the population currently eligible for this treatment, i.e., persons with AF, increased risk of ischemic stroke and contraindication to oral anticoagulation (OAC). Two of the studies included in the thesis (referred to below as studies I and II) investigate the stroke preventive effect of LAAO and its cost-effectiveness in this subpopulation.

As mentioned above, a large share of the stroke-related cost is due to informal care. Today, it is not common practice to include the cost of informal care in health economic evaluations, and more evidence on the consequences of informal care is needed. Previous studies have reported that informal caregivers have an increased risk of cardiovascular diseases,[6] often report mental health disorders,[7-9] and have lower self-reported health.[9] However, whether the decreased health among informal caregivers translates into changes in their healthcare utilisation has not been investigated. It has also been reported that informal caregivers of persons with stroke are likelier to leave their employment after the stroke onset.[10] But there is little evidence of how the change in employment status affects their financial situation. Because these outcomes are connected to economic consequences and therefore informative for handling informal care in health economic evaluations, studies III and IV focus on informal caregivers of persons with stroke and consequences for healthcare utilisation and the financial situation.

1.1 STRUCTURE OF THE THESIS

The thesis starts with a chapter on *stroke* containing a general description of stroke, which is the main disease area of this thesis. The subsequent chapter is *atrial fibrillation*, which gives a general overview of AF and the importance of stroke prevention among persons with AF, this chapter aims to give the reader the necessary knowledge and rationale for studies I & II. The following chapter, *informal care*, describes what is known about informal caregivers' health and financial situation and, more importantly, what is not known. Further, the costs related to informal care in general and the cost of informal care for persons with stroke are described, and the inclusion of informal care in health economic evaluations. This chapter gives a rationale for studies III & IV, focusing on spouses of persons with stroke healthcare utilisation and income. The overall aim and the aim for the individual studies I-IV is presented in the *Aim* chapter. The chapter *Material and method* describe the different data sources, study populations, and methods used in each study included in this thesis. The results of studies I-IV are described separately in the *Result* chapter. In the *Discussion* chapter, each study I-IV is discussed in relation to the overall aim of the thesis. The main conclusion of the thesis is presented in the *Conclusion* chapter. Lastly, the thesis contains a chapter on *Future perspectives*.

2 STROKE

Stroke is a cardiovascular disease (CVD) which results in neurological symptoms such as paresis, aphasia and vision or sensory loss due to the disruption of blood circulation that occurs during a stroke.[11] There can be different causes of stroke; most strokes are caused by a blood clot (thrombus), which limits the blood flow to or in the brain and is the underlying cause in 62% of strokes globally.[12] This is referred to as an ischemic stroke. The remaining strokes are due to a haemorrhage in the brain or between the meninges.[12] In 2021, 27 000 strokes (including both ischemic and haemorrhagic strokes) were reported among 25 400 persons in Sweden, i.e., some persons had more than one stroke.[13] Globally, stroke is one of the diseases causing the most mortality and disability,[2] and about 50% have remaining disabilities.[12] The disability and dependency in daily activities after stroke can be measured by the modified Rankin Scale (mRS).[14] mRS is measured on a scale from zero to six, and its classification is presented in Box 1:[14]

Box 1. mRS classification

0	No dependency in daily activities
1	No disability but have symptoms. The person can carry out daily activities independently
2	Some disabilities, the person can carry out their own affairs independently; however, they are not able to carry out all daily activities as usual
3	Moderate disability, the person needs some support in daily activities; however, they can walk independently
4	Moderate severe disability, the person cannot walk independently and depends on assistance with bodily need
5	Severe disabilities, the person is bedridden, incontinent and dependent on constant assistance from others
6	Dead

In previous research reporting the dependency in daily activities after stroke using mRS, it is often categorised as no dependency if mRS 0-2 and dependency in daily activities if mRS 3-5.

3 ATRIAL FIBRILLATION

Atrial fibrillation is one of the most common heart arrhythmias, which causes a quick irregular heart rhythm and dysfunctional synchronisation of atrial muscle contraction. The global prevalence is estimated to be between 2 and 4%.[15] AF may lead to incomplete atrial emptying of blood and increase the risk of formation of blood clots, which can cause, for example, ischemic stroke. In the AF population, the risk of ischemic stroke is five-fold; therefore, stroke prevention is one essential cornerstone in managing AF.[15] Other vital parts of the management of AF are; "*symptom management"* and *"cardiovascular risk factors and concomitant diseases"*[15]. Stroke preventive treatment in persons with AF depends on the risk of ischemic stroke and bleeding. The risk of ischemic stroke is usually measured on a scale from 0-9 by the risk assessment tool CHA^2DS^2-VAS, which is based on existing risk factors.[16] The risk factors included in the CHA^2DS^2-VASc instrument are presented in Box 2.

Box 2. The risk factors included in the CHA^2DS^2-VASc instrument

CHA^2DS^2-VASc		
Letter	**Risk factor**	**Score**
C	Congestive heart failure	1
H	Hypertension	1
A	Age ≥75	2
D	Diabetes Mellitus	1
S	Stroke	2
V	Vascular disease	1
A	Age 65-74	1
S	Sex (women)	1

3.1 STROKE PREVENTION IN PERSONS WITH ATRIAL FIBRILLATION

Among persons with AF, there are several options for stroke preventive treatment, and stroke prevention can be either primary or secondary. The most common are non-vitamin-K antagonist oral anticoagulants (NOAC) and vitamin-K antagonists (VKA), which are included under the umbrella expression OAC. NOAC is comparably effective in preventing ischemic stroke as VKA. Further, NOACs are associated with a lower risk of haemorrhagic

stroke and all-cause mortality than VKA; however, the risk of gastrointestinal bleeding increases with NOACs.[17] The stroke preventive effect of antiplatelet treatment (APT) has been investigated. According to previous research, APT has been unsuccessful in preventing stroke in patients with AF compared to no antithrombotic treatment (OACs or APT).[18] Further, when comparing dual antiplatelet treatment (DAPT) to APT, the risk of thromboembolic events such as ischemic stroke and systemic emboli decreased, but with a significant increase in major bleeding.[19]

According to the European Society of Cardiology (ESC) guidelines for the diagnosis and management of AF developed in collaboration with the European Association for Cardio-Thoracic Surgery (later referred to as the European guidelines),[15] stroke prevention with NOAC is recommended over VKA (except for patients with mechanical heart valves or moderate/severe mitral stenosis). At a CHA^2DS^2-VASc ≥2 for men and ≥3 for women, stroke prevention with OAC is recommended. APT or DAPT is not recommended as stroke prevention for patients with AF.[15] Similarly, the national guidelines for cardiology in Sweden recommend the use of NOAC over VKA for persons with AF and CHA^2DS^2-VASc VASc ≥2 for men and ≥3 for women,[20] and APT should not be used as stroke prevention for persons with AF and increased risk of ischemic stroke.[20]

As mentioned above, OAC effectively prevents ischemic stroke; however, OAC is related to adverse events such as haemorrhagic stroke and gastrointestinal bleeding. This makes some persons ineligible for OAC as they have absolute or relative contraindications such as active bleeding, comorbidities (severe thrombocytopenia or severe anaemia), or recent intracranial haemorrhage (ICH). How large share of the population with AF that have contraindications to OAC is not clearly described. However, one possible way of estimating the number of persons with AF and contraindications to OAC is by the proportion of persons with AF, not prescribed OAC as secondary prevention after an ischemic stroke. According to the Swedish stroke register, 19% of persons with AF and ischemic stroke were not prescribed OAC as secondary prevention after the stroke event.[21]

For persons with long-term contraindications to OAC, there is no optimal pharmaceutical stroke preventive treatment. The current standard of care for persons with AF, increased risk of ischemic stroke and contraindication to OAC is no pharmacological antithrombotic treatment. However, according to the European guidelines, LAAO may be recommended as stroke prevention for this subpopulation of persons with AF.[15]

3.1.1 CLINICAL EFFECTIVENESS FOR PERSONS WITH AF AND CONTRAINDICATIONS TO OAC

Percutaneous endocardial LAAO is an intervention where a medical device is inserted into the left atrial appendage (LAA) to reduce the risk of thrombus. It has previously been reported that 90% of the thrombi originate from the LAA in persons with AF.[22] These thrombi can later cause an ischemic stroke. The previous literature is based on the randomised controlled trials (RCT) PROTECT-AF[23] and PREVAIL.[24] The PROTECT-AF and PREVAIL trials only include individuals with AF who are eligible for long-term OAC. In other words, the RCTs[23,24] excluded persons with contraindications to OAC, i.e. the population who can be recommended LAAO as stroke prevention according to current European guidelines. Ongoing RCTs are estimating the effect of LAAO among persons ineligible for long-term OAC.[25,26] For example, the COMPARE LAAO trial randomises persons to LAAO or to continue current optimal medical treatment, which could consist of APT or no treatment.[25] To my knowledge, there are currently no completed RCTs that report the clinical effectiveness of LAAO among persons with AF, increased risk of stroke and contraindication to OAC. A few systematic reviews and meta-analyses estimate the clinical effectiveness of LAAO based on the current literature (observational studies and RCTs).[27-29] Nevertheless, none of these systematic reviews and meta-analyses focuses on the subpopulation of persons with AF and contraindications to OAC.

There is a growing literature of observational studies that reports on the effect of LAAO in AF patients with contraindications to OAC. While waiting for the RCT to report their results, there is a need to estimate the clinical effect of LAAO in the published literature. Therefore, study I aimed to estimate the long-term clinical effectiveness of LAAO in individuals with AF, increased risk of ischemic stroke and contraindication to OAC in a systematic review and meta-analysis of observational studies.

3.1.2 ESTIMATING THE COST-EFFECTIVENESS OF TREATMENTS

Health economic evaluations are often divided into two main categories, health economic evaluations alongside clinical trials and health economic evaluations using decision-analytic modelling. Several different types of analyses can be conducted within health economic evaluations. The general concept is that two or more alternative interventions are compared regarding costs and consequences (health effects). Different analyses used in health economic evaluations are cost-minimisation, cost-effectiveness, and cost-benefits analysis (description in Box 3.). Quality-Adjusted Life-Years (QALYs) are often used as the effect measure in health economic evaluations. QALYs are a generic measurement, which makes it possible to prioritise between treatments and disease areas.[30] Further, QALY is a multidimensional measurement that considers Health-related Quality of Life (HRQoL) (typically estimated by generic instruments such as EuroQol 5 dimensions 3 levels (EQ-5D-3L)) and time.[30]

Box 3. Description of different analyses used in health economic evaluations

Cost-minimisation analysis can be used when the outcome measure between the different alternatives is similar in terms of effects. Therefore, only costs are included in the analysis.

Cost-benefit analysis is an analysis where both costs and effects are measured in monetary terms.

Cost-effectiveness analysis estimates costs in monetary terms and effects in natural units (such as blood pressure (mmhg)), HRQoL or QALY, which takes HRQoL and time into consideration.

The cost-effectiveness of an intervention can be measured based on the incremental cost-effectiveness ratio (ICER). The ICER is calculated from four components, the average cost and QALY (one example of health effect) per patient in each treatment alternative. From these components, the incremental cost and QALY are estimated. Finally, the incremental cost is divided by the incremental QALYs. The ICER can be interpreted as the cost for one additional QALY with treatment A compared to treatment B.[30] Whether the intervention under investigation is cost-effective depends on the willingness to pay (WTP) for a QALY. The WTP can be illustrated as a threshold value, i.e., if the ICER is below the threshold value, it is considered cost-effective.

3.1.3 COST-EFFECTIVENESS OF LAAO FOR PERSONS WITH AF AND CONTRAINDICATIONS TO OAC

The current evidence on the cost-effectiveness of LAAO for persons with AF and contraindications to OAC is scarce. Percutaneous LAAO is related to a relatively expensive implementation cost, and it is crucial to establish the cost-effectiveness of LAAO. To my knowledge, there is no published health economic evaluation of LAAO in patients with AF, increased risk of ischemic stroke and contraindication to OAC that is carried out alongside a clinical trial. However, one study by Saw et al.[31] estimates the cost-effectiveness of LAAO compared to APT in persons with AF and contraindication to OAC, using a decision-analytic model (Markov model). Saw et al.[31] based the risk of ischemic stroke after LAAO on a relatively small study, and they do not include any costs related to nursing homes or home care. In another study, Reddy et al.[32] estimated the cost-effectiveness of LAAO compared to APT and Apixaban (NOAC) in persons with AF and contraindication to warfarin using a Markov model. The risk of ischemic stroke is based on the result of the PROTECT-AF trial (excluding persons with contraindications). Both Saw et al.,[31] and Reddy et al.[32] reports that LAAO is cost-effective compared to APT over a lifelong time horizon and a 10-year period, respectively. When estimating the cost-effectiveness of an intervention, the choice of the comparator is critical. According to the European[15] and Swedish guidelines,[20] APT should not be considered as stroke prevention in this population and would therefore not make a relevant comparator for LAAO.

This knowledge gap is addressed in study II, which estimates the cost-effectiveness of LAAO compared to the standard of care (no pharmacological antithrombotic treatment) among persons with AF, increased risk of ischemic stroke and contraindication for OAC using the risk of ischemic stroke estimated in study I. In addition, the analysis is made from a healthcare and public sector perspective, i.e., including the costs of special housing and home care in Sweden.

4 INFORMAL CARE

Informal care is when a person provides support with everyday tasks such as meals, dressing, transportation, and emotional support. The informal caregiver can be a relative, for example, a spouse, an adult child, or a sibling. The informal caregiver can also be someone within the person's social network, such as a neighbour or friend. Verbakel[33] investigated the amount of informal care given and its correlation to long-term formal care in 19 European countries and found that, on average, around 34% and 7% of the study population carried out informal care and intensive informal care (>11 hours/week).[33] Informal caregivers in the Nordic countries (Denmark, Finland, Norway, and Sweden) provided more than average informal care compared to the other included European countries; however, the Nordic countries provided less than average intensive informal care[33]. Concerning long-term formal care, Verbakel[33] reports that countries with more formal long-term care had a higher prevalence of informal care, while the prevalence of intensive informal care decreased.[33]

The burden of informal care can depend on several factors, such as the relationship between the person who receives and carries out informal care, if the informal care is given inside or outside the household, and the severity of the disease. Spousal informal caregivers report a higher caregiver burden, carrying out more hours of informal care per week than adult child informal caregivers.[34] In a study by Broese van Groenou et al.,[34] 69% of adult child informal caregivers received support from other informal caregivers, while only 20% of spouses received support from other informal caregivers. Further, only 22% of spouses reported receiving support from formal home care. In contrast, 54% of adult child informal caregivers reported receiving support from formal home care.[34] The time spent on informal care can also depend on the severity of the disease. Persson et al.[35] found that spouses of persons with stroke and mRS 3-5 carried out more informal care than spouses of persons with stroke and mRS 0-2.[35]

4.1 INFORMAL CAREGIVERS' HEALTH

Being an informal caregiver can negatively affect health. A large European study by Kaschowitz & Brandt[36] investigated the effect on self-reported general health and depressive symptoms depending on whether informal care was given inside or outside the household. Persons who carried out informal care inside the household had lower general health and were more depressed than non-informal caregivers. In comparison, persons who carried out informal care outside the household reported better general health than the non-informal caregivers.[36] It has also been reported that informal caregivers have an increased risk of CVD compared to non-informal caregivers.[6] One possible explanation for this could be spousal concordance, i.e., that spouses share lifestyle and health behaviour. Spousal concordance has been described in several cardiovascular risk factors; smoking habits,[37] body mass index (BMI),[37] hypertension,[38] and diabetes.[39]

Mental disorders such as anxiety are common among informal caregivers of persons with stroke.[7-9] Further, spouses of persons with stroke and mRS 3-5, i.e., dependent in daily activities, score lower on the general health domain in the generic instrument 36-items short-form health survey (SF-36) compared with spouses of persons with stroke who are independent in daily activities and the control population.[40] Lastly, spouses of persons with stroke also have an increased risk of all-cause death five years after the stroke event of their partner.[41]

4.2 INFORMAL CAREGIVERS' HEALTHCARE UTILISATION

Whether the adverse effects seen on informal caregivers' health transfer into a change in healthcare utilisation is not fully understood. One could hypothesise that informal caregivers' healthcare utilisation might increase due to adverse health. However, it is also possible that the informal caregiver does not seek healthcare as their health is not prioritised. The results from previous studies vary: n o differences have been found between informal caregivers and non-informal caregivers regarding the time from the last routine check-up,[42] the number of healthcare contacts[42] or health insurance billings,[43] but it has also been reported that informal caregivers use more healthcare resources, such as emergency room visits[44] and outpatient visits.[45,46] Most research on informal caregivers' healthcare utilisation focuses on the informal caregiver of persons with dementia or self-reported informal caregivers, i.e., not informal caregivers to a person with a specific disease. As mentioned above, informal caregivers of persons with stroke report adverse health effects. However, to the author's knowledge, there is no research studying whether these effects translate into changes in healthcare utilisation for informal caregivers of persons with stroke.

4.3 INFORMAL CAREGIVERS' FINANCIAL SITUATION

Informal caregivers of working age might have to adjust their working life to manage their role as an informal caregiver. It has previously been reported by Grigorovich et al.[47] that working-age spouses of persons with stroke are negatively affected in their daily life, education possibilities, and ability to work. When studying the effect on spouses' employment when their partner's working situation changes, two mechanisms are often discussed: the *"added worker effect"*[48] and the *"caregiver effect"*.[49] The "*added worker effect*" was first described among married women whose husbands became unemployed. It refers to when spouses increase their work to compensate for the loss of their partner's unemployment.[48] In contrast, the *"caregiver effect"* refers to when an informal caregiver decreases their work to manage the role as an informal caregiver.[49]

Jeon and Pohl[50] have investigated the effect on spouses of persons with cancer employment and earnings. They described that spouses' employment and earnings decrease after the cancer diagnosis of their partner. Further, they report that the effect on employment, earning, and combined family income seen among women spouses is larger than among men.[50]

In contrast, García-Gómez et al.,[51] who studied employment and disposable income among spouses of persons with acute hospitalisation, found the largest decrease in employment and disposable income among male spouses.[51]

The research on informal caregivers of persons with stroke and the associated effect on employment and earnings is limited. Persson et al.[10] have previously reported that compared to a reference population, spouses of persons with stroke were more likely to stop working after their partner's stroke event. This effect was even more notable among young spouses. Jeon et al.[52] compared employment and earnings among spouses of persons with stroke to a reference population in Canada. They found that younger spouses and spouses of persons with severe stroke were more likely to cease working and earn less. However, in the overall population of spouses of persons with stroke, they did not find any differences.[52] The effect on spouses of persons with stroke earnings was investigated as the percentage change between income groups and not as the loss in earnings in absolute numbers,[52] which is necessary if the estimates should be used in health economic evaluations.

4.4 COSTS OF INFORMAL CARE

A large share of stroke-related costs is due to informal care. Out of the total stroke-related cost in the EU in 2015, 35% (16 billion) was related to the informal care of persons with stroke.[3] Ekman et al.[53] estimated the cost of informal care in Sweden, divided into direct and indirect costs. The direct costs of caregiving included costs due to time spent on informal caregiving, out-of-pocket expenditures, and lost sleep. While the indirect costs included costs related to work cessation, reduced work hours, and reduced working productivity. The total annual cost of informal care was estimated to be 152 billion Swedish kronor (SEK) and 128 000 SEK per informal caregiver. Of these 152 billion SEK, 45% was direct costs, and 55% was indirect costs.[53]

4.4.1 COSTS OF INFORMAL CARE OF PERSONS WITH STROKE

A study that estimated the cost of informal care based on the number of hours spent on informal caregiving the first-year post-stroke in France estimated a mean cost of 4 607 EUR and 25 200 EUR for persons with stroke and mRS 0-2 (independent in daily activities) and mRS 3-5 (dependent in daily activities), respectively.[54] Persson et al.[35] estimated the cost of informal care for persons with stroke, including practical support, support in contact, housework and being available. The annual cost of informal care of persons with stroke and mRS 0-2 was estimated to be 991 EUR and 25 127 EUR for persons with stroke and mRS 3-5.[35]

4.4.2 INFORMAL CARE IN HEALTH ECONOMIC EVALUATIONS

When carrying out health economic evaluation, one of the first steps is setting the frame of the analysis, i.e., which perspective the analysis should apply. The perspective of the analysis determines which costs and health effects are to be included. The analysis result is highly dependent on the chosen perspective, e.g., what can be cost-effective from one perspective may not be cost-effective from another perspective.

A common perspective is the *healthcare perspective*, which means that costs and health effects that appear within the healthcare sector are included. Another common perspective is the *societal perspective* which should include all relevant costs and health effects in all sectors of society regardless of the payer.

When authorities make an assessment for reimbursement, the perspectives of the health economic analysis differ (Table 1.).[55-59] The Dental and Pharmaceutical Benefits Board Agency (TLV)[57] in Sweden, The Danish Medicines Council (DMC),[55] The National Institute for Health and Care Excellence (NICE)[58] in the UK, and The Norwegian Medicines Agency (NOMA)[59] have moved away from including the cost of productivity loss for patients. In contrast, the authorities consider some costs and health effects for informal caregivers. An overview of the cost and health effects taken into consideration by five authorities is presented in Table 1. The role of including costs and health effects of informal caregivers in health economic evaluations will be discussed later in this thesis.

Table 1. An overview of the inclusion of costs and health effects related to informal care in health economic evaluations informing reimbursement decisions of pharmaceuticals in five authorities based on their guidelines.

Country	Perspective	Cost of informal caregivers	Health effects of informal caregivers
Denmark	Limited societal perspective	Costs related to transportation and time due to the treatment should be included.	Potential changes in HRQoL can be described and are considered in the overall decision. However, it should not be included in the health economic evaluation.
Finland	Not stated	Loss of time and productivity.	It should not be included in the base case analysis. However, it can be included in a sensitivity analysis.
United Kingdom	NHS or personal social service perspective	Time spent on caregiving; however, the analysis should be presented separately.	Outcomes such as HRQoL that are relevant to informal caregivers
Norway	Extended health service perspective	Prevention or treatment costs, which the informal caregiver pays. Transportation cost and time spent related to treatment.	If relevant, HRQoL can be considered, and the analysis must be presented with and without the HRQoL of informal caregivers.
Sweden	Societal perspective	Costs can be considered	Not specified

Abbreviation: HRQoL Health-Related Quality of Life, NHS National Health Service

4.4.3 COST OF INFORMAL CARE IN HEALTH ECONOMIC EVALUATION

When valuing the resource use in health economic evaluations, it is, in theory, valued according to the opportunity cost, i.e., the missed benefits when resources are not used on the second-best alternative.[30] The opportunity cost can be identified in functioning markets by the market price of the resource. In practice, market prices are applied when available. For resource use where market prices are unavailable, the valuation can be conducted in different ways.

The valuation of the productivity loss due to informal care can be conducted by the human capital method. In the human capital approach, production loss costs are estimated until the individual can return to work and are based on the gross wage and social fees.[30]

Different methods can be used when valuing the time spent on informal care, for example, by the opportunity cost.[30] Another method could be to value informal caregiving based on the market wages of the tasks carried out by the informal caregiver, which can be referred to as the proxy good method (PGM).[30] For example, if the informal caregiver carries out a task that a nurse could do, the value of informal care equals the nurse's wage.

4.4.4 HEALTH ECONOMIC EVALUATIONS INCLUDING INFORMAL CARE

Two separately conducted systematic reviews by Goodrich et al.[60] and Krol et al.[61] (no overlap in included studies) aimed to investigate to what extent informal care was included in health economic evaluations, the methods used to estimate cost and consequences and how the inclusion of informal care affected the results of the health economic evaluation. The systematic review by Krol et al.[61] only included studies related to specific disease areas (Alzheimer's disease, Rheumatoid arthritis, Parkinson's disease or metastatic colorectal cancer). Both systematic reviews state that a small share of the screened health economic evaluations included costs and/or consequences of informal care. Out of the 30 studies included in Goodrich et al.,[60] 25 included costs related to informal care, while 12 out of 23 included studies by Krol et al.,[61] reported costs related to informal care. In both systematic reviews, there were discrepancies in the method used to value these costs. The method used for the valuation of the cost was either the opportunity cost method or the PGM. It was less common to include the health consequences of informal care.[60,61] The method used to measure the consequences differed, and QALYs were estimated in half of the included studies.[60]

A more recent systematic review by Scope et al.[62] focused on health economic evaluations, including the health effects of informal caregivers and family members.[62] They identified 40 studies that included health effects estimated as QALYs between 1999 and 2021, and 15 of the 40 studies focused on child vaccination. The systematic reviews[60-62] concluded that inclusion cost and/-or health effects of informal caregivers can affect the results of the health economic evaluation. However, to what extent differed between the included studies. Further, the importance of considering the feasibility of including informal care in each specific health economic evaluation is raised, and a key suggestion from the authors of the review articles is that when informal care is left out, a justification is needed.[60,61]

In summary, the consequences of spouses of persons with stroke are understudied, specifically whether the adverse health and the increased risk of cessation of work translate into changes in healthcare utilisation and financial situation. Also, the potential impact of including these consequences among spouses of persons with stroke in health economic evaluations is unknown. Therefore, study III investigates the healthcare utilisation among spouses of persons with stroke, while in study IV, spouses' financial situation is investigated.

5 AIM

The overall aim of this thesis was to investigate two health economic aspects of stroke: (i) the clinical and cost-effectiveness of stroke prevention with LAAO among persons with AF and contraindications to OAC, (ii) the long-term consequences of stroke on spouses' healthcare utilisation and financial situation and its potential impact in health economic evaluations.

The thesis includes four studies that each contribute to the overall aim. The specific aim of each study was:

Study I: To determine the clinical effectiveness of LAAO as stroke prevention in persons with AF, increased risk of ischemic stroke and contraindication to OAC.

Study II: To estimate the cost-effectiveness of LAAO as stroke prevention for persons with AF, increased risk of ischemic stroke and contraindication to OAC compared to standard of care from a Swedish perspective.

Study III: To assess the long-term effect on healthcare utilisation among spouses of persons with first-ever stroke in Sweden and the long-term effect on healthcare utilisation among spouses based on the dependency in daily activities of the person with stroke.

Study IV: To investigate the long-term financial consequences for spouses of persons with first-ever stroke in Sweden. Further, the study aims to estimate spouses' long-term financial consequences according to the age and sex of the spouse and dependency in daily activities of the person with stroke.

6 MATERIAL AND METHOD

The studies included in the thesis use a variety of study designs and analysis methods. The different study designs and analyses used in the specific studies are presented in Table 2.

Table 2. Overview of the study design and primary analysis

	Study design	Primary analysis
Study I	Systematic review	Meta-analysis
Study II	Combined decision tree and Markov model	Cost-effectiveness analysis
Study III	Longitudinal register study	Difference-in-differences
Study IV	Longitudinal register study	Difference-in-differences

6.1 DATA COLLECTION AND STUDY POPULATION

The Swedish register infrastructure consists of national, regional, and quality (disease-specific) registries. Registries can be linked and create data material for research through the Swedish personal identification number.[63] The following subchapters describe the different registries used in studies II-IV, followed by a description of the study populations.

6.1.1 STATISTICS SWEDEN

Statistics Sweden is the registry holder for several national registries containing sociodemographic data, such as the register of the total population (RTB) and the Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA).

RTB is the core of Statistics Sweden's individual-level register and is based on information from the Swedish tax agency. RTB includes all individuals registered in Sweden, contains demographic information, and is updated annually.[64] Statistics Sweden's LISA register is also an individual-level register which is based on several sources such as RTB, education of the population register (UREG), income and taxation register (IoT), and labour market register (RAMS). LISA includes individuals 15 years and older who are registered in Sweden.[65]

In studies III & IV, demographics such as age, gender, civil status, and educational level from the LISA register were applied. In addition, in study IV, the income variables, income (individual income from paid work), disposable individual income, and disposable family income, were received from the LISA register (Table 3.).

6.1.2 THE SWEDISH STROKE REGISTER

The Swedish Stroke Register is a national quality register for stroke-related healthcare in Sweden and includes information on persons with stroke and transient ischemic attack (TIA). The Swedish Stroke Register collects data about the initial hospitalisation and outcomes, such as support from relatives and dependency in daily activities at three months and one year after the stroke event.[66,67] In 2010 and 2011, The Swedish Stroke Register covered 88%[66] and 90.5%[67] of all strokes, respectively, and 88% of these were followed-up at three months. For studies III & IV, information was collected regarding the initial hospitalisation and the three-month follow-up of persons with first-ever stroke in 2010 and 2011 (Table 3.).

6.1.3 NATIONAL BOARD OF HEALTH AND WELFARE

The National Board of Health and Welfare is the registry holder for several national health-related registries in Sweden, and one of these is the National Patient Register. The National Patient Register receives data from Sweden's 21 regions.[68] Full national coverage of all public inpatient and specialised outpatient care in Sweden was reached in 1987 and 2001, respectively. The information related to specialised outpatient care is limited because it only covers physician visits.[68] In study III, information on the length of the hospital stay from the National Patient Register was used (Table 3.).

6.1.4 REGIONAL HEALTHCARE REGISTRIES

In Sweden, some regional healthcare registries allow researchers to apply for healthcare data. Two of these regional healthcare registries are the regional healthcare register in Region Västra Götaland and Region Skåne. The regional healthcare register in Region Västra Götaland[69] and Region Skåne[70] contains information on specialised outpatient care and primary care, with no limitation on which healthcare personnel the patient visited. When estimating the effect on spouses' healthcare utilisation in study III, the number of visits to primary and specialised outpatient care from the regional healthcare registries in Region Västra Götaland and Skåne were used (Table 3.).

Table 3. Overview of the use of registries and variables in studies II-IV

	Study II	Study III	Study IV
Statistics Sweden (RTB & LISA)			
Demographics		X	X
Income			X
Disposable individual income			X
Disposable family income			X
The Swedish Stroke Register			
Demographics of the person with stroke		X	X
mRS of the person with stroke	X	X	X
Health-related quality of life of the person with stroke	X		
The National Board of Health and Welfare			
Number of days with inpatient care		X	
Regional healthcare registries			
Number of visits to specialised outpatient care		X	
Number of visits to primary care		X	

6.2 STUDY POPULATION

6.2.1 STUDIES I AND II

In studies I and II, the population under investigation is persons with AF, increased risk of ischemic stroke and contraindication to OAC.

Study I is a systematic review and meta-analysis based on secondary data, i.e., already published studies. Therefore, the only criteria for the study population in study I was persons with AF and contraindication to OAC. In study II, the study population is a hypothetical cohort. The cohort's baseline characteristics are based on study I's results. At baseline, the cohort consisted of persons with AF, an increased risk of ischemic stroke, and contraindication to OAC. The increased risk of ischemic stroke is based on CHA^2DS^2-VASc, and a CHA^2DS^2-VASc of 4 in the study population and a mean age of 74, was assumed in the cohort.

6.2.2 STUDIES III AND IV

In studies III and IV, the primary study population consisted of spouses of persons with first-ever stroke in 2010 or 2011. The person with stroke was retrieved from The Swedish Stroke Register; after that, Statistics Sweden identified their spouses (according to Statistics Sweden's definition of family). Spouses to the person with stroke could be identified if they were married, were registered partners, or had shared biological or adoptive children, i.e., it was not possible to identify unmarried couples who were co-living without having biological or adoptive children. The primary study population also consisted of a reference population. Each spouse was matched with four reference individuals according to age, sex, and municipality of residence by Statistics Sweden.

Study III estimated the long-term effect on spouses' healthcare utilisation. The entire population of spouses and their reference population was used to analyse the effect of the number of days with inpatient care from the National Patient Register. However, when analysing the visits in primary and specialised outpatient care, the study population was narrowed down to spouses (and reference population) living in Region Västra Götaland or Region Skåne during the year of the stroke event. This limitation was made since I only had access to primary and specialised outpatient care in those two regions. In study IV, the study population is based on the national study population used in study III, but with a restriction in age. Since I wanted to investigate spouses' financial consequences during the five-year follow-up, spouses older than 60 at the stroke event year were excluded so that the study population is of working age during the entire study period.

6.3 STUDY DESIGN AND ANALYSIS METHOD

6.3.1 SYSTEMATIC REVIEW AND META-ANALYSIS

In study I, a systematic review and meta-analysis were conducted to estimate the long-term clinical effectiveness of LAAO among persons with AF, increased risk of ischemic stroke, and contraindications to OAC.

Systematic review

A systematic review aims to systematically gather and synthesise information to answer a research question, following a predefined structure.[71] The first step in conducting a systematic review and meta-analysis is formulating the review question.[72] When the review question is clearly formulated, criteria for inclusion and exclusion are stated. An essential part of this step is formulating the PICO, which stands for **p**atient, **i**ntervention, **c**ontrol and **o**utcome.[73] The PICO for study I is presented in Box 4.

Box 4. The PICO for study I

Population	Persons with AF, increased risk of ischemic stroke and contraindication to OAC
Intervention	Percutaneous endocardial LAAO
Control	Not applicable due to missing comparators in the published studies
Outcomes	Primary outcome was ischemic stroke. Further, TIA, major bleeding and all-cause mortality was included as secondary outcomes

The search strategy needs to be defined when inclusion and exclusion criteria are determined. As recommended, a biomedical librarian was consulted to plan the search strategy, i.e., choose databases and search strings.[74] After carrying out the planned search strategy, I started to select studies to include in the systematic review and meta-analysis. According to the recommendation, titles and abstracts were screened for potentially relevant studies to include. The full-text article was screened for studies with a relevant abstract. When all relevant studies were screened in full text, the final decision of inclusion was made.[74]

Documenting the process of identification, screening, and decisions is crucial. I used the recommended: The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow chart[74] to report the process of selecting studies.

After deciding which studies were eligible for the systematic review and meta-analysis, data extraction was performed. As recommended by Li et al.,[75] study characteristics and outcomes were extracted, and the variables to extract were decided beforehand.[75] In study I, data was extracted into the following categories: study characteristics, patient characteristics, device and outcomes, where each category had several variables.

Meta-analysis

A meta-analysis is conducted to synthesise the outcome from two or more studies, potentially increasing the estimate's precision. A meta-analysis is often conducted using either a fixed-effect or random-effects model. In a fixed-effects model, it is assumed that there is one true effect in all studies investigating the intervention. In contrast, the random-effect model assumes that the true effect can follow a distribution and vary in each study included in the meta-analysis.[76]

Depending on the characteristics of the outcome variable extracted, different methods can be used. From the systematic review in study I, the number of events from each study was extracted to obtain a pooled estimate of ischemic strokes per 100 person-years in the study population. When dealing with count data in a meta-analysis, the main choice is the inverse-variance method or Poisson regression.[76] Since several studies included in the meta-analysis had zero ischemic stroke events or counts close to zero, a random-effect Poisson regression was chosen as the primary analysis method as it does not require adding an arbitrary constant to handle studies with zero events.[77] The exposure variable was person-years, and the output from the Poisson regression model was an incidence rate. In study I, the results from the Poisson regression was reported as the number of ischemic strokes per 100 person-years.

Study I also aimed to compare the pooled estimates from the meta-analysis to the predicted risk of ischemic stroke with no pharmacological stroke prevention at CHA^2DS^2-VASc 4. A CHA^2DS^2-VASc of 4 was chosen since a CHA^2DS^2-VASc around 4 was commonly reported in studies investigating the population receiving LAAO treatment. The predicted risk of ischemic stroke without any pharmacological stroke prevention was based on a study by Friberg et al.,[78] which reports the predicted risk of ischemic stroke at different CHA^2DS^2-VASc, based on 90 490 persons with AF in Sweden. To make this comparison, I needed to predict the incidence rate of ischemic stroke at

CHA^2DS^2-VASc 4 in the data material. This was done using a Poisson meta-regression, where the CHA^2DS^2-VASc score was added as a covariate to the meta-analysis model.

When several studies are compiled in a meta-analysis, studies to some extent differ from each other, which can result in heterogeneity in the observed treatment effect.[76] The heterogeneity in systematic review and meta-analysis can be measured using a chi-square test (chi^2), where the results from the chi^2 test are reported as I^2. If the I^2 indicates heterogeneity, the heterogeneity should be addressed. Deeks et al.[76] report threshold values which can be used to interpret the I^2, where 30-60% represent moderate heterogeneity, 50-90% substantial heterogeneity, and 75-100% considerable heterogeneity. However, when interpreting I^2, the confidence interval (CI) and the output (p-value) from the chi^2 test should be considered.[76]

6.3.2 DECISION-ANALYTIC MODELS

Decision tree and Markov model

In study II, the cost-effectiveness of LAAO, compared to the standard of care in Sweden, was estimated using a decision-analytic model consisting of a combined decision tree and Markov model. The cost-effectiveness analysis is carried out from a Swedish healthcare and public sector perspective. The healthcare perspective includes costs related to the healthcare sector, while the public sector perspective includes costs and effects in the healthcare sector and costs related to special housing and home care financed by the municipality.

Both decision trees and Markov models are commonly used decision-analytic models, and both can be used as cohort models. In a cohort model, a hypothetical cohort of the average patient for the intervention under investigation is characterised.[79] In study II, the cohort consists of persons with AF, increased risk of ischemic stroke and contraindication to OAC, and a mean age of 74 at the model start and a CHA^2DS^2-VASc of 4, which is based on the results from study I.

The decision tree is one of the most basic types of decision-analytic models. The cohort moves from left to right through the different pathways in the decision tree based on the probability of the different events. A shortcoming of the decision tree is that time is not naturally included in the model, and it can be hard to manage a decision tree if it includes many pathways or repeated events.[79] In study II, the decision tree was used during the first year of the decision-analytic model. Its main aim was to estimate the first-year cost of the LAAO and allocate the cohort into a successful or unsuccessful LAAO

procedure. The LAAO procedure is considered unsuccessful if a device cannot be inserted in the left atrial appendage due to, for example, anatomical reasons.

The cohort enters the assigned Markov model from the second year of the decision-analytic model. A Markov model simplifies reality; however, the intention is that the health states included in the model should correspond to the disease progression without the treatment under investigation.[80] The Markov model in study II consisted of eleven health states: ischemic stroke-free survival, all-cause mortality, and three ischemic stroke health states separated according to mRS categories; similarly, recurrent ischemic stroke and post-ischemic stroke health states were divided based on mRS categories. When mRS is used to describe the dependency after stroke in the studies included in this thesis, mRS is divided into three categories: mRS 0-2 (no dependency), mRS 3 (moderate dependency) and mRS 4-5 (severe dependency). The reason for this division is as mRS 3 is different in the level of dependency from mRS 4-5, and by having mRS 3 as a separate category, more precise costs and effects can be estimated.

How long the cohort stays in a health state depends on the cycle length. The cohort can move between health states in a Markov model at each cycle. The cycle length should be based on, for example, the nature of the disease, i.e. transitions from one health state to another should be permitted according to the nature of the disease.[80] At which speed the cohort moves through the Markov model depends on the transition probabilities (based on the probability of the clinical events).

Each health state in the model is associated with a mean cost and health effect, adjusted by the cycle length. The number of cycles that the model includes depends on the time horizon. The time horizon should be long enough to capture all costs and effects related to the intervention under investigation. A lifelong time horizon should be applied if the treatment affects mortality.[79,80] Since LAAO treatment potentially indirectly affects mortality by preventing stroke, a lifelong time horizon is applied.

The average cost, health effects, and transition probabilities in a Markov model are based on different sources and mainly on secondary data.[79] In study II, several sources to populate the model were used, such as the risk of ischemic stroke[1] estimated in study I, previous research, cost from a hospital and registry

[1] In the Markov model, the risk of ischemic stroke (rate), is not converted into a probability. However, when converting this rate to a probability, there is only a minimal change in the input values and does not affect the interpretation of the results.

data. For example, to estimate the QALY-decrements in the ischemic stroke, recurrent ischemic and post-ischemic stroke health states, I used a dataset from The Swedish Stroke Register, including persons with ischemic stroke in 2010-2011. I calculated the QALY-weight for each person in the dataset according to the mapping procedure by Ghatnekar et al.,[81] which used the response from five questions at the 3-month follow-up. Lastly, I calculated the mean QALY-weight in each mRS category, i.e., mRS 0-2, mRS 3 and mRS 4-5.

After running the decision tree and Markov model, the mean expected cost and QALY per patient with LAAO and the standard of care were estimated separately. Finally, the ICER was calculated, which is interpreted as the additional cost per QALY with LAAO compared to the standard of care. In study II, the commonly used threshold value for cost-effectiveness analysis of 500 000 SEK[82] (45 828 EUR) was applied.

Sensitivity analysis

When using a decision-analytic model, it is crucial to explore the parameter uncertainty and the potential effect on the result.[79] To investigate the parameter uncertainty in study II, a one-way deterministic sensitivity analysis (DSA), a probabilistic sensitivity analysis (PSA) and scenario analyses were conducted. In the one-way DSA, one input parameter at a time was changed (all other parameters kept at base case value) to see how a decrease or increase in the parameter affected the result. In study II, all parameters were included in the one-way DSA, and the input parameters were changed by ±20%. In contrast, when carrying out PSA, all parameter values change simultaneously, within a range, and are repeated at least 1 000 times. The range was calculated based on the input parameter's standard error, and each range was given a distribution based on the characteristics of the parameter. The PSA results in many simulated incremental costs and health effects, enabling an estimation of the probability of an intervention being cost-effective.

A sequence of different scenarios is created in a scenario analysis, for example, best- or worst-case scenario analysis.[83] Two of the most uncertain parameters in study II were the risk of ischemic stroke with LAAO (treatment effect which is estimated to be 74.7% in study I) and the mRS distribution after an ischemic stroke, i.e., in the base case LAAO treatment results in less person with stroke and mRS 3 (moderate dependency in daily activities) and mRS 4-5 (dependent in daily activities). I wanted to explore the needed treatment effect for LAAO to remain cost-effective if it instead was assumed that after LAAO treatment, the distribution of mRS categories was similar between LAAO and the standard of care. Therefore, an equal mRS distribution (between LAAO and the standard of care) was assumed and simultaneously, the treatment effect was lowered to 50%, 25% and until LAAO was no longer considered cost-effective.

6.3.3 DIFFERENCE-IN-DIFFERENCES ANALYSIS

In studies III and IV, a difference-in-differences approach was used to estimate the long-term effect on spouses of persons with stroke healthcare utilisation (study III) and financial situation (study IV).

Difference-in-differences is a quasi-experimental method that can estimate causal effects in panel data assuming certain conditions are met (see below).[84] A quasi-experimental design means no formal randomisation of treatment; instead, researchers use natural experiments to estimate effects. When using a difference-in-differences method, two groups are needed, one group is exposed to an event, and one is unexposed. In studies III and IV, the exposed group consists of spouses of persons with a first-ever stroke in 2010 or 2011, and the unexposed group consists of a reference population who is not a spouse to a person with stroke in 2010 or 2011. As the name suggests, the difference-in-differences method consists of two differences, (i) the average difference in the outcome before and after the event in both groups and (ii) the difference between the groups. The event in studies III and IV is the stroke onset of the person with stroke, and to measure the differences before and after differences among spouses and the reference population. I have registry data for 2005-2016, i.e., five years before and after the stroke event of the persons with stroke.

One critical assumption when using a difference-in-differences method is the parallel trend assumption.[84] This means that in the absence of the event, both the exposed and unexposed groups would have followed the same trend in the post-period, which is untestable. However, to judge if the parallel trend assumption may hold, it is instead common to inspect the trends in the pre-period, which were done in study III. In study IV, an event study[85] to test the pre-event trends and visually inspect the pre-event trends was conducted.

In study III, a violation against the parallel trend assumption was suspected, so propensity score-weighted analyses were conducted. In the propensity score-weighted analyses, the reference population was re-weighted to equal the spouses in the pre-period[86]. The propensity score for each outcome was estimated separately through a logistic regression where the pre-period outcomes were the independent variable, and the dependent variable was a categorical variable representing the spouse or reference population.

Subgroup analysis

In both studies III and IV, several subgroup analyses were carried out. In both studies, subgroup analyses were conducted based on the mRS of the person with stroke. In addition to the analysis based on the mRS of the person with stroke, I also conducted subgroup analyses based on spouses' age and sex in study IV. Sex is categorised as *men* and *women,* and age is separated into two groups *≤50* and *>50* years old.

6.3.4 ETHICAL APPROVAL

No ethical approval was sought for study I since it only used already published studies. Regarding study II, although it is primarily based on secondary published data, ethical approval was sought and approved for the parts of the study that required aggregating individual-level data, e.g., estimating the mRS distribution and estimating the proportion of the cohort with changed living arrangements. This information is based on the dataset from The Swedish Stroke Register (Dnr: 813-17 & Dnr: 2019-03535).

For studies III and IV, ethical approval was sought and approved (Dnr: 813-17 & Dnr: 2019-03535).

7 RESULTS

7.1 LONG-TERM CLINICAL EFFECTIVENESS OF LAAO

A systematic review and meta-analysis were conducted to estimate the clinical effectiveness of LAAO in persons with AF, increased risk of ischemic stroke, and contraindication to OAC (study I).

The systematic review and meta-analysis included 29 observational studies without controls,[87-114], which resulted in a total of 7 951 person-years. The weighted mean follow-up of the included studies was 1.46 years. The average age and CHA^2DS^2-VASc score in the study population were 74 and 4.32, respectively.

The pooled incidence rate of ischemic stroke from the random-effects Poisson regression was 1.38 (95% CI): 1.08; 1.77), and I^2 was 48%, i.e., moderate heterogeneity.[76] The predicted incidence rate of ischemic stroke at CHA^2DS^2-VASc 4 after LAAO, from the meta-regression, was 1.39 (95% CI: 0.95; 2.02). The predicted incidence rate of ischemic stroke was compared to the predicted risk of ischemic stroke at CHA^2DS^2-VASc 4 without any pharmacological stroke prevention (5.5 ischemic stroke/100 person-years).[78] This resulted in a reduction of the incidence rate of ischemic stroke by 74.7% (Figure 1.).

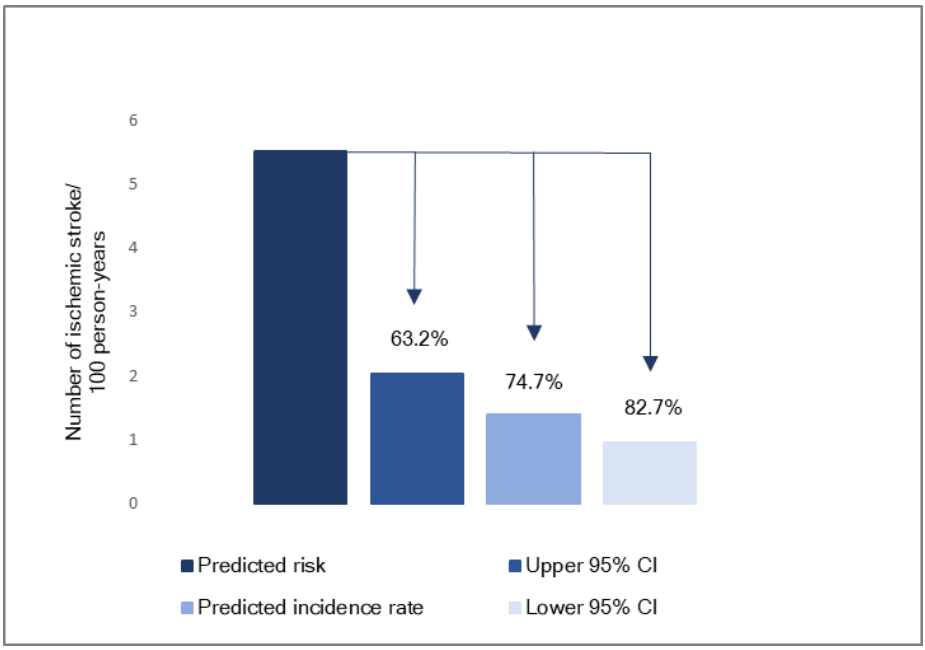

Figure 1. Estimated risk reduction of ischemic stroke at CHA^2DS^2-VASc 4 from the meta-regression, together with the upper and lower bound of the confidence interval compared to the predicted risk of ischemic stroke.

7.2 COST-EFFECTIVENESS OF LAAO

In study II, a cost-effectiveness analysis of LAAO compared to the standard of care in Sweden was conducted. According to the decision-analytic model, LAAO was associated with a mean cost per patient of 19 032 EUR and 21 029 EUR from the healthcare and public sector perspectives, respectively. The mean cost per patient with the standard of care was 15 022 EUR and 31 281 EUR. This results in an additional incremental cost with LAAO of 4 010 EUR, compared to the standard of care from a healthcare perspective. On the other hand, LAAO costs, on average, 10 252 EUR less than the standard of care from a public sector perspective. Further, LAAO treatment resulted in an increase of 0.99 QALYs on average compared to the standard of care.

Based on the incremental cost and QALY, the ICER for LAAO compared to the standard of care was 4 047 EUR per QALY gained from the healthcare perspective. As seen in Figure 2., the ICER was in the upper right quadrant of the cost-effectiveness plane (i.e., more costly and more effective). Further, the ICER was located below the commonly applied threshold value of 45 829 EUR (500 000 SEK) per QALY gained in Sweden. Therefore, LAAO was considered cost-effective compared to the standard of care from a healthcare

perspective. Since LAAO was less costly and resulted in more QALYs compared to the standard of care from a public sector perspective, the ICER was in the lower right quadrant of the cost-effectiveness plane (Figure 2.). ICERs located in the lower right quadrant are always considered cost-effective.

In Study II, a range of sensitivity analyses was carried out: DSA, PSA, and scenario analyses. The results were robust to changes (±20%) in the input parameters, i.e., these changes did not change the interpretation of the results. The result from the PSA is depicted together with the base case ICER in Figure 2. showing that from a healthcare perspective, all simulated ICERs remained below the threshold value. From a public sector perspective, more than 99% of the simulated ICERs were in the lower right quadrant (i.e., lower cost and more QALYs). In the scenario analysis, equal distribution of mRS for both LAAO and standard of care was applied, and a reduced treatment effect of LAAO. The treatment effect could be lowered to 25% (from 74.7% in the base case) before the ICER was located above the threshold and no longer considered cost-effective from a healthcare perspective. In comparison, from a public sector perspective, LAAO treatment was considered cost-effective until the treatment effect was lowered to 20%.

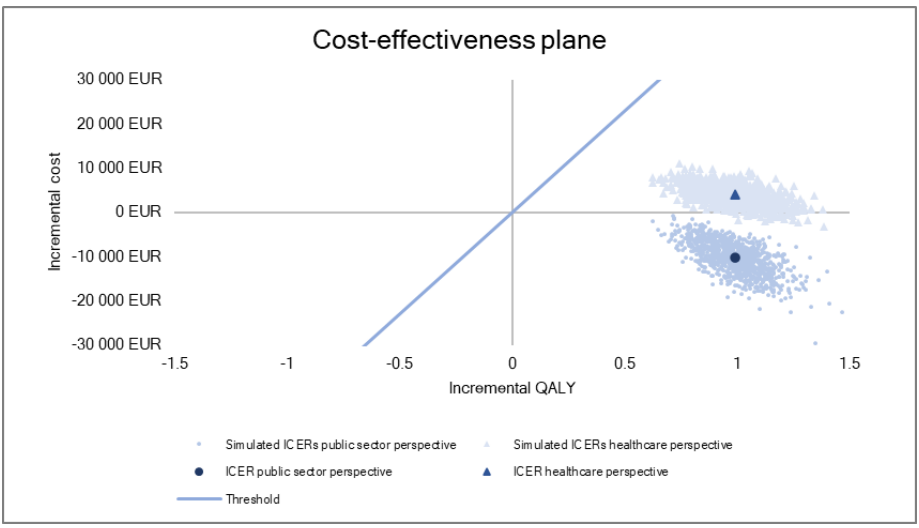

Figure 2. The cost-effectiveness plane presents the ICERs from the healthcare and public sector perspective, the simulated ICERs from the PSA, and the cost-effectiveness threshold.

7.3 EFFECTS ON SPOUSES OF PERSONS WITH STROKE HEALTHCARE UTILISATION

Study III estimated the long-term effects on spouses of persons with stroke healthcare utilisation.

This study was based on two separate study samples, the national study sample, used when analysing the days with inpatient care. The national sample consists of approximately 13 000 spouses of persons with stroke and 52 000 in the reference population. The second sample, which was used when analysing the primary and specialised outpatient care in Region Västra Götaland and Region Skåne, consists of about 4 000 spouses and 15 500 in the reference population. Both groups were comparable concerning age, sex, country of birth and disposable income (detailed information is available in study III).

The primary analysis showed that, on average, spouses of persons with stroke have 0.09 (95% CI: 0.01; 0.17) more days with inpatient care during the five years following their partner's stroke event, compared to the reference population. This is equivalent to a 5.8% (95% CI: 1% to 12%) relative increase in the number of days with inpatient care, and in the absence of the stroke event, spouses would have 1.52 days with inpatient care instead of 1.6 (Figure 3.). On the other hand, the results indicate that spouses of persons with stroke had fewer visits to primary and specialised outpatient care compared with the reference populations. However, these differences were statistically insignificant.

In the analyses based on mRS, the largest relative change (compared to the reference population) in the number of days to specialised outpatient care (7.7%) and days with inpatient care (7.7%) was identified among spouses to persons with stroke and mRS 3. In contrast, the largest relative change regarding the number of visits to primary care (4.9%) was identified among spouses of persons with stroke and mRS 4-5. However, none of the analyses based on mRS was statistically significant. The relative changes in healthcare utilisation based on mRS are presented in Figure 3.

The result from the propensity-score weighted analysis was comparable to the unweighted results, both regarding the main analysis and the analysis based on mRS.

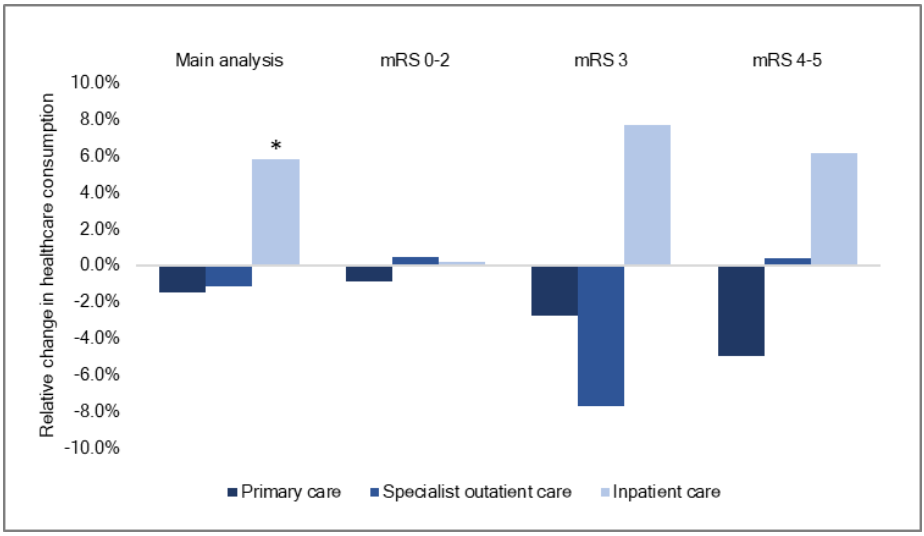

Figure 3. The relative change in healthcare utilisation in the main analysis and the analyses based on mRS.
** Statistically significant, p-value <0.05.*

7.4 EFFECTS ON SPOUSES OF PERSONS WITH STROKE FINANCIAL SITUATION

Study IV estimated the effect on working-age spouses of persons with stroke financial situation using a difference-in-difference approach. The study population consisted of about 2 500 spouses of persons with stroke and 9 500 persons in the reference population. In study IV, spouses were less likely to be born in Sweden, and a larger share had less than a high school education.

According to the result, spouses of persons with stroke disposable family income decreased during the five years after their partner's stroke onset (p <0.001). A decrease in income and disposable individual income was also identified; however, this decrease was minor and statistically insignificant (Figure 4.).

In the subgroup analysis based on mRS, a statistically significant increase in income (2 868 EUR) and disposable individual income (4 409 EUR) was identified among spouses of persons with stroke and mRS 4-5 (Figure 4.). Further, the results from the subgroup analyses based on age and sex showed that the most affected spouses were women aged 50 or below. Younger women spouses' disposable family income decreased by 6 877 EUR (p <0.001) and their individual income by 1 614 EUR (p=0.008) on average after the stroke onset of their partner; however, a corresponding decrease in disposable

individual income was not seen (Figure 4.). No statistically significant difference was identified when analysing the effect on income and disposable individual income among male spouses.

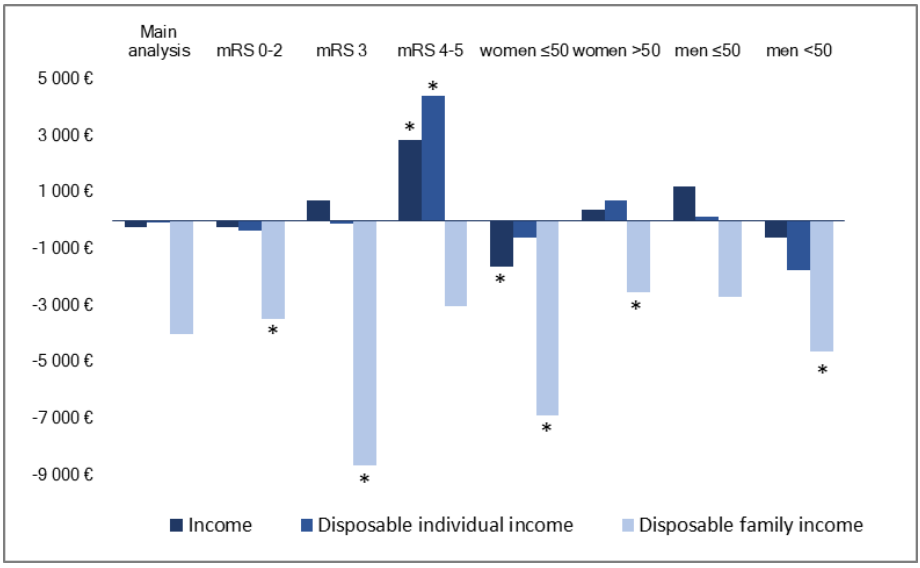

Figure 4. Result from the main analysis and subgroup analyses according to mRS and sex and age.
** Statistically significant, p-value <0.05.*

8 DISCUSSION

This thesis aimed to investigate two health economic aspects of stroke and, more specifically, the clinical and cost-effectiveness of a stroke preventive intervention (LAAO) among persons with AF, increased risk of stroke and contraindication to OAC. Further, this thesis aimed to investigate the long-term consequences of stroke on spouses' healthcare utilisation and financial situation and its potential impact in health economic evaluations.

8.1 CLINICAL AND COST-EFFECTIVENESS OF LAAO

Stroke is a common disease and one of the diseases that causes the most disability and mortality. As mentioned previously, stroke is also a costly disease for society, and many strokes are preventable. Preventing strokes can lead to less stroke-related disability, mortality, and societal cost. It is essential to have effective stroke preventive treatments; further, it is important that these treatments are cost-effective. Studies I and II contribute with valuable evidence of the clinical and cost-effectiveness of LAAO as stroke prevention among persons with AF, increased risk of ischemic stroke and contraindication to OAC.

8.1.1 CLINICAL EFFECTIVENESS OF LAAO

In study I, the clinical effectiveness of LAAO as stroke prevention among persons with AF, increased risk of ischemic stroke, and contraindication to OAC was estimated. The predicted incidence rate of ischemic stroke at CHA^2DS^2-VASc 4 from the meta-regression was 1.39/100 person-years. This resulted in a risk reduction of 74.7%, compared to the predicted risk score (5.5/100 person-years) at CHA^2DS^2-VASc 4. The two systematic reviews and meta-analyses[27,28] that estimated the incidence rate of ischemic stroke after LAAO in the overall population receiving LAAO reported slightly lower incidence rates of 1.1/100 person-years and 1.0/100 person-year. Busu et al.[29] compared the observed versus the expected risk of ischemic stroke in a systematic review and meta-analysis and reported a risk reduction of 73.7%. Their study population is comparable to study I in several aspects, such as age, CHA^2DS^2-VASc and HAS-BLED. However, Busu et al.[29] included all patient populations receiving LAAO. According to current European guidelines, only persons with contraindications to OAC can be recommended LAAO. Study I only included studies focusing on patients with contraindications to OAC and therefore contributed with valuable clinical effectiveness evidence for precisely this population.

8.1.2 COST-EFFECTIVENESS OF LAAO

According to the cost-effectiveness analysis in study II, LAAO is cost-effective compared to the standard of care from a Swedish healthcare and public sector perspective. Even though there are several differences between study II and the previously published cost-effectiveness analysis of LAAO among persons with contraindications,[31,32] similar conclusion was reached. The main differences are the choice of perspective, comparator and in which population the treatment effect was estimated. In study II, a broader perspective (public sector perspective) was applied and included costs related to nursing homes and home care. Further, in study II, LAAO was compared to the current standard of care in Sweden for the subpopulation of persons with AF and contraindications to OAC. One of the main strengths of study II compared to previously published cost-effectiveness analyses[31,32] is that the stroke preventive effect of LAAO is based on a large sample of persons with AF and contraindications to OAC.

Both study II and the other two cost-effectiveness analyses use decision-analytic models. Even though these health economic evaluations use different data sources, assumptions, patient populations and comparators, similar conclusions were drawn, i.e., that LAAO can be considered cost-effective. As mentioned previously, no published results from the RCTs focus on persons with contraindications to OAC. Therefore, no health economic evaluation of LAAO has been conducted alongside clinical trials. Until such evidence becomes available, study II contributes with valuable information for decision-makers on the cost-effectiveness of LAAO for a subpopulation of persons with AF with contraindications to OAC. Further, the scenario analysis suggests that the stroke preventive effect of LAAO can be lower than estimated in study I before LAAO is no longer considered cost-effective in this subpopulation. However, the result of study II must be confirmed by the results from health economic evaluations alongside the ongoing clinical trials.

8.2 SPOUSES OF PERSONS WITH STROKE HEALTHCARE UTILISATION AND FINANCIAL SITUATION

It has previously been reported that informal caregivers of persons with stroke health are adversely affected,[7-9,41] and their working situation changes.[10,52] However, to what extent these adverse health effects translate into changes in healthcare utilisation has been an understudied research topic. Similarly, even though the previous literature suggests that spouses of persons with stroke are more likely to stop working after the stroke event, there has been no evidence of the financial consequences for the spouse of the person with stroke.

It is important to increase the knowledge about the consequences for several reasons, such as understanding the actual consequences for the spouse and the potential societal cost due to increased healthcare utilisation and productivity loss. Further, it is valuable to estimate these effects to determine the potential importance of including these consequences in health economic evaluations of stroke interventions.

8.2.1 SPOUSES' HEALTHCARE UTILISATION

The previous literature on healthcare utilisation of informal caregivers is mixed, i.e., some studies report no difference,[42,43] while others report an increase in healthcare utilisation.[44-46] Nevertheless, none of these studies has investigated healthcare utilisation among spouses of persons with stroke. The results from study III suggests that the effect on spouses of persons with stroke healthcare utilisation is relatively small, and the direction of the change in healthcare utilisation depends on the type of healthcare contact analysed and the mRS of the person with stroke. However, in the main analysis of study III, a statistically significant increase in the number of days with inpatient care was identified among spouses of persons with stroke. This is aligned with previous findings that informal caregivers utilise more healthcare resources than non-informal caregiver.[45,46,115]

In contrast, the number of visits to primary and specialised outpatient care among spouses of persons with stroke decreased after the stroke event; however, this decrease was not statistically significant. A previous study based on the same study population identified an increased risk of all-cause mortality among spouses of persons with stroke.[41] One would hypothesise that the increased mortality would have been foregone by an increased number of healthcare contacts. However, according to the results from study III, this is not entirely the case. One possible explanation could be that spouses of persons with stroke do not prioritise their health and healthcare needs. Therefore, a decrease in primary and specialist outpatient care was seen, while inpatient care, where an increase was identified, is often unavoidable.

In addition, study III expands the analysis of spouses of persons with stroke healthcare utilisation by analysing it in subgroups based on the mRS of the person with stroke. In the analyses based on mRS, the biggest relative change in primary care was seen among spouses of persons with stroke and mRS 4-5. Further, the largest relative change in specialised outpatient care (7.7% decrease) and inpatient care (7.7% increase) was identified among spouses of persons with mRS 3. Note that these estimates are imprecise, i.e., they have wide confidence intervals, and interpretation should be made cautiously. Similarly, as with the main analysis, one could debate that one possible reason for the decrease in specialised outpatient care is that the spouse does not

prioritise their health and that specialised outpatient care visits are often possible to deprioritise. In contrast, inpatient care is often unavoidable. There can be several possible explanations for the most considerable relative change regarding specialised outpatient and inpatient care among spouses of persons with mRS 3. One explanation is that spouses of persons with mRS 3 might have the highest caregiver burden. Persons with stroke and mRS 3 often live at home but need support to manage daily activities, while persons with stroke and mRS 4-5 more often change their residence to special housing.

8.2.2 SPOUSES' FINANCIAL SITUATION

In the primary analysis of study IV, a statistically significant decrease in disposable family income was identified. This decrease is likely driven by the person with stroke's loss of income since a corresponding decrease in spouses' income or disposable individual income is not seen. Putting the results from study IV into the Swedish context is relevant. Even though Sweden carries out slightly more than average hours of informal care compared to other European countries, Sweden is one of the countries that carry out the least amount of intensive informal care, where intensive informal care is defined as more than 11 hours per week of informal care.[33] Further, according to Verbakel,[33] Sweden is the most generous country regarding formal care in Europe, where formal care is measured by, for example, the number of long-term care beds and healthcare workers per 1000 population ≥65. The low number of intensive informal caregivers, combined with available formal care, might contribute to the fact that no large effects on income are seen in study IV. However, these results might not be generalisable to other contexts.

These results are similar to the findings by Jeon and Pohl,[50] who reported the largest effect on spouses' individual income and family income among women spouses of persons with cancer. In the analysis in study II, according to age and sex, a statistically significant decrease in income and disposable family income was identified when the spouse was a younger woman (≤50 years). It has previously been reported by Estrada-Fernández et al.[116] that a larger share of women informal caregivers in the Nordic countries carries out more than >2 hours/week of informal care than men. This could be one possible explanation of why the income from paid work is most affected among younger female spouses. Moreover, a statistically significant decrease in disposable individual income was not identified. The disposable individual income summarises the different social insurances (such as sickness benefits & benefits for taking care of a relative) available in Sweden and the income from paid work. This indicates that social insurance may cover a part of the loss of income from paid work.

In the subgroup analysis based on mRS, a statistically significant increase in income and disposable individual income was identified among spouses of persons with stroke and mRS 4-5. One explanation for this could be that persons with mRS 4-5 often move to special housing, which could make it possible for the spouse to increase their work hours to cover up for the loss of income of the person with stroke. This finding somewhat contradicts Jeon et al.,[52] who report that spouses of persons with severe stroke were more likely to stop working and earn less. However, there are differences between mRS and how they define severe stroke. Jeon et al.,[52] define severe stroke as needing intensive care, mechanical ventilation and length of the hospital stay, and not the dependency in daily activities.

8.2.3 INCLUDING INFORMAL CARE IN HEALTH ECONOMIC EVALUATIONS

The possible importance of including costs related to informal care in health economic evaluations is an ongoing discussion. When informal care consequences are included in health economic evaluations, it often focuses on the time spent on informal care and-/or HRQoL.[60-62] However, other consequences might be relevant to include in health economic evaluations, such as healthcare utilisation and loss of productivity. In study III, a slight increase (0.09 or 5.8% relative change) in the number of days with inpatient care was identified. Due to data limitations, it was impossible to estimate the change in cost related to healthcare utilisation from the data material. Applying a unit price of 7 100 SEK[117] per day at a general internal medicine ward would result in an additional cost of 627 SEK per spouse and year related to inpatient care. Even though the additional cost seems small, it is a real consequence and cost, and if a societal perspective is applied, it should, in theory, be included. However, it would, in many cases, have a limited impact on the results of the health economic evaluation of stroke treatments. Including the cost of spouses' additional inpatient care (assuming that 65% have a spouse, based on the proportion in study III) in the cost-effectiveness analysis in study II only has a minor impact on the results. The ICER from the public sector perspective (similar to the societal perspective but without the productivity loss) changes from -10 347 EUR to -10 405 EUR.

According to the results from study IV, the individual financial situation of the spouses of persons with stroke is not affected to a large extent. In the overall population of spouses, no statistically significant differences were identified. Including spouses' financial situation in health economic evaluations of stroke treatments might not be of great importance. In addition, it might not be relevant to include productivity loss for other reasons. Several health technology assessments (HTA) agencies exclude productivity loss of the

patient due to ethical reasons, i.e., not discriminating against patients outside of the workforce and including loss of productivity of spouses could be seen as contradictive.

8.2.4 OTHER IMPLICATIONS

There are also other areas where these findings are important. For example, the results could be of clinical value as they suggest that spouses of persons with mRS 3-5 are more affected than spouses of persons with stroke and mRS 0-2. Similarly, that younger female spouses are affected to a larger extent. Further, even though studies III and IV identify small and mostly statistically insignificant changes in the overall population of spouses of persons with stroke, these results provide valuable information for future cost-of-illness studies. As mentioned in the subchapter above, the additional cost for inpatient care among spouses of persons with stroke is relatively small. However, it could be worth considering the incidence of persons with stroke in Sweden resulting in a high number of spouses of persons with stroke. In Sweden, approximately 20 000 persons have a first-ever stroke each year, and by assuming that about 65% of persons with stroke have a spouse. This can lead to a considerable cost on a societal level.

Further, this information about the consequences in the different subgroups and the increased resource use (inpatient care) contribute with valuable information for decision-makers when the healthcare sector design and implement interventions directed towards spouses of persons with stroke.

8.3 METHODOLOGICAL CONSIDERATIONS

8.3.1 CLINICAL EFFECTIVENESS OF LAAO

When conducting a systematic review, it is recommended that two independent researchers carry out the screening process. However, according to the Cochrane Handbook for Systematic Reviews of Interventions,[118] it is sufficient that only one researcher carry out the title and abstract screening. In study I, one independent researcher conducted all screening and data extraction. This could be considered a limitation of the study, and there is a risk that studies have been missed. To decrease the risk of missing highly relevant studies, the reference list of all studies included in study I was screened. Regarding the data extraction, the data extraction mainly consisted of retrieving baseline characteristics and the number of events from tables, with a minimal need for interpretation. There is a risk that studies have been missed or errors have been made during data extraction; however, the probability that these errors are of the magnitude that the interpretations of study I changes is small.

Comparing the estimated incidence rate of ischemic stroke to a predicted risk score can be considered a limitation due to two reasons, (i) no confidence interval was reported for the predicted risk score, (ii) unobservable confounder between the two populations compared. In study I, the predicted incidence rate of ischemic stroke at CHA^2DS^2-VASc 4 from the meta-regression was compared to a predicted risk score by Friberg et al.[78] They based the predicted risk score on a population of 90 490 persons with AF in Sweden, and the predicted risk of ischemic stroke (strokes/100 person-years) at each CHA^2DS^2-VASc was presented. As mentioned above, no 95% confidence interval is reported. Therefore, when the uncertainty of the reduced risk of ischemic stroke was estimated in study I, this was done based on the 95% CI of the predicted incidence rate of ischemic stroke from the meta-regression. Further, there was a risk of unobservable confounders; however, the comparison is made between persons with AF and CHA^2DS^2-VASc 4 in both populations, and some essential risk factors are considered, suggesting that the populations are comparable. However, differences between the populations, which are not considered in the CHA^2DS^2-VASc instrument, could still exist and affect the estimated reduction of ischemic stroke after LAAO.

8.3.2 COST-EFFECTIVENESS OF LAAO

As there is a lack of published results from RCTs focusing on persons with AF, increased risk of ischemic stroke and contraindication to OAC, the cost-effectiveness analysis in study II was conducted using a combined decision tree and Markov model. Decision-analytic models simplify reality, and the model in study II has some shortcomings. For example, the model does not include any health states related to major bleeding, which could have been relevant since this patient population often have an increased bleeding risk. As APT increases the risk of major bleeding, post-procedural treatment with APT could contribute to more major bleeding after LAAO. However, in the model, the post-procedural treatment with APT was only prescribed for six months. Including an increased risk of bleeding during a half cycle would probably have had a limited impact on the long-term results.

When using a decision-analytic model, secondary data from several sources are used. One concern is how well the population in the secondary sources matches the population in the model. When selecting the secondary data sources, the literature was thoroughly screened to identify the best possible choice of the secondary data source.

Nonetheless, some concerns remain. For instance, the secondary source to estimate the distribution of mRS among the LAAO cohort was based on the PROTECT-AF trial, which is suboptimal in several ways. One of the reasons is that the patients with contraindications were excluded from the study and

had warfarin as a post-procedural treatment for six months. Further, the CHA^2DS^2-VASc in the PROTECT-AF were 3.4, implying a lower risk of ischemic stroke compared to the population in the model. These factors might affect the mRS distribution after LAAO (LAAO results in ischemic strokes with less dependency in daily activities mRS 3-5); however, no studies describing the mRS distribution after LAAO among persons with contraindication were identified.

The potential problems with comparing the risk of ischemic stroke from study I with a predicted risk score have been discussed previously. Since both the risk of ischemic stroke with LAAO and the mRS distribution after ischemic stroke are associated with uncertainties and the main drivers of the cost-effectiveness of LAAO, extensive sensitivity analyses were carried out. In the scenario analysis, I assumed similar mRS distribution for both LAAO and the standard of care and simultaneously lowered the treatment effect (74.7% in the base case). The treatment effect could be lowered to 25% and 20 % from a healthcare perspective and public sector perspective before LAAO was no longer considered cost-effective. Further, the scenario analysis could also possibly be used as a benchmark when the treatment effect from the ongoing RCTs is published.

8.3.3 SPOUSES OF PERSONS WITH STROKE

Spouses of persons with stroke are identified through Statistics Sweden's RTB registry, and spouses should be possible to identify if married, registered partners or having joint children (biological or adoptive). Spouses living together with a person with stroke in an apartment building without joint children were impossible to identify. This identification strategy missed spouses living together but not having joint children. However, during the work with study IV, it was noticed that only 2% of the reference population was unmarried, and all spouses were married in the year of the stroke event. The reason for this is currently unknown; however, it is unlikely that no couples live together and have shared children without marriage. The population only includes married spouses and not cohabitant spouses with shared children, which affects the generalisability of the results, i.e., the results from studies III and IV would be only generalisable to married spouses.

Both studies III and IV were based on registries and used a difference-in-differences approach. When a difference-in-differences approach is used, one of the most essential assumptions is the parallel trend assumption. This means that in the absence of the stroke event, both the spouses of persons with stroke and the reference population would follow the same trend. However, it is impossible to test if the trends are parallel in the absence of the stroke event. Therefore, it is common to investigate if parallel trends exist in the time period

before the event (pre-period) and then assume that in the absence of the event, the groups will follow the same trend in the following time period. If there are existing parallel trends in the pre-period can be measured in several ways, such as plotting the trends in the pre-period followed by a subjective judgment if the trends are parallel or not. Another more objective option is to conduct an event study and test if there is a statistically significant difference in the trends in the pre-period between the groups.[85] In study III, where a violation of the parallel trends is suspected, this was only measured by looking at the plots. A better solution might have been to conduct an event study to test the pre-trends more objectively, as it was done later in study IV. However, in study III, when the reference population where re-weighted in the pre-period to handle the possible violation of the parallel trend assumption, this did not affect the results of the study in a considerable way.

8.4 ETHICAL CONSIDERATIONS

Studies I and II mainly used data from secondary data sources and did not require approval from an ethical board. However, other ethical aspects are essential to consider as a researcher. In study I, which only aggregated secondary data from other already published studies, the risk of causing harm to the individual included in the studies included in the systematic review and meta-analysis is minimal.

In study II, which is also primarily based on data from secondary data sources, the risk of causing harm to the individual included in the secondary data sources is very small. Further, the information from the Swedish Stroke Register is only presented on an aggregated level, and it is impossible to identify specific individuals.

Studies III and IV are registry studies where I have had access to individual-level data, which statistics Sweden has deidentified. However, when handling this kind of sensitive information, it must be handled and reported cautiously. Both studies have large sample sizes, and the results were only presented on an aggregated level, making it nearly impossible to identify a specific individual from the results reported.

Even though the benefits of these studies overshadow the risk of causing harm to the individual in the studies, there are other potential aspects to consider as a researcher. It is essential to consider the implications of the results presented in the studies and how that could affect potential decision-makers. For example, studies I and II report a positive result of the clinical effectiveness and cost-effectiveness of LAAO as stroke prevention. Suppose these results have unintentionally been overestimated, and persons receive this treatment,

and it later is proven that LAAO is not as effective as first estimated. In that case, it can negatively affect the persons receiving the treatment and society.

One ethical consideration that is worth considering regarding the possible inclusion of spousal consequences in health economic evaluations is the risk of discriminating patient population that is less likely to have a spouse. This could disadvantage treatments directed toward diseases or patient populations with a smaller share of the population having a spouse.

9 CONCLUSION

This thesis has highlighted two essential and unstudied health economic aspects of stroke from a Swedish perspective. The first two studies provide evidence that LAAO reduces the risk of ischemic stroke and is cost-effective as stroke prevention for a subpopulation of persons with AF and supports the current guidelines in Europe.

The results from studies III and IV suggest that the effect on healthcare utilisation and financial situation for spouses of persons with stroke are relatively small. Including these aspects in health economic evaluation of stroke interventions would most likely have limited impact on the results. However, some subpopulations, such as younger women, appear to be more affected, which warrants further consideration in practice and future research.

10 FUTURE PERSPECTIVES

Studies I and II conclude that LAAO can be considered clinically and cost-effective among persons with AF, increased risk of ischemic stroke, and contraindication to OAC. Even though these studies contribute with valuable information, they also have some limitations and interesting research areas that were out of the scope of these studies.

It is essential to validate the clinical effectiveness reported in observational studies with RCTs. One essential RCT is the COMPARE LAAO trial[25], where LAAO is compared to standard of care (no treatment or single or double APT) among persons with AF, increased risk of ischemic stroke and is deemed unsuitable for OAC. The post-procedural treatment after LAAO is DAPT for three months, followed by APT for at least one year.[25] The post-procedural treatment after LAAO is vital to decrease the risk of device-related thrombosis (DRT), which could later cause an ischemic stroke. Post-procedural treatment can possibly affect the incidence rate of ischemic stroke after LAAO. In study I, the post-procedure treatments differed between the included studies (APT, DAPT, NOAC or VKA). Since it was outside the scope of study I, none of the analyses was carried out according to the post-procedure treatments. To the author's knowledge, there are no consensus or general recommendations regarding the post-procedure treatments. However, it is important to investigate the effect of different post-procedural treatments in future research.

One of the limitations of study II is that the mRS distribution after stroke among persons with contraindication to OAC that received LAAO is based on the PROTECT-AF trial, which indicates that persons who receive LAAO have fewer disabling strokes (mRS 3-5). However, the mRS distribution after a stroke among persons with contraindications that received LAAO treatment is not known and is an important topic for future research.

Even though RCTs are often considered the “gold standard” in research, when estimating the cost-effectiveness of LAAO treatment, a lifelong time horizon is most likely needed. Since RCTs often have a shorter time horizon, there will most likely be a need to combine the results from the RCTs with decision-analytic models, such as Markov modelling, to estimate the long-term cost-effectiveness of LAAO in future studies.

Studies III and IV suggest that including spouses of persons with stroke healthcare utilisation and financial situation would have limited impact on the results of health economic evaluations. However, there are other important aspects to consider. For example, the mRS of the person with stroke seems to

affect to what extent and direction spouses' healthcare utilisation and financial situation are affected. It would be valuable to estimate these effects among spouses based on the mRS of the persons with stroke in studies with larger sample sizes to get more precise estimates in future studies.

In future studies, it would be interesting to estimate the change in actual healthcare costs among spouses of persons with stroke and not only the number of visits or days with inpatient care. As mentioned in the discussion, there is only a small change in healthcare utilisation. However, when briefly calculating the cost for this slight increase in the number of days with inpatient care, it could be associated with a considerable cost for society.

Further, related to both studies III and IV, it would be valuable to complement these studies with qualitative research to get a deeper understanding of the mechanism surrounding healthcare utilisation and the financial situation among the overall population of spouses of persons with stroke. But also to explore the underlying mechanism of the heterogeneity identified based on age, gender and the mRS of the person with stroke.

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