European Heart Journal (2022) **43**, 1348–1356
https://doi.org/10.1093/eurheartj/ehab847

CLINICAL RESEARCH
Interventional cardiology

Cost-effectiveness analysis of left atrial appendage occlusion in patients with atrial fibrillation and contraindication to oral anticoagulation

Frida Labori [1]*, Josefine Persson [1], Carl Bonander [1], Katarina Jood [2,3], and Mikael Svensson [1]

[1]Health Economics and Policy, School of Public Health and Community Medicine, Institute of Medicine, University of Gothenburg, Box 463, Gothenburg 405 30, Sweden; [2]Institute of Neuroscience and Physiology, Department of Clinical Neuroscience, The Sahlgrenska Academy at University of Gothenburg, Sahlgrenska University Hospital, Blå stråket 7, Gothenburg 413 45, Sweden; and [3]Region Västra Götaland, Sahlgrenska University Hospital, Department of Neurology, Blå Stråket 7, Gothenburg 413 45, Sweden

Received 2 July 2021; revised 8 September 2021; editorial decision 26 November 2021; accepted 29 November 2021; online publish-ahead-of-print 17 December 2021

See the editorial comment for this article 'Left atrial appendage occlusion in patients unable to tolerate anticoagulation is cost-effective in Sweden: but how generalizable is this finding?', by Amneet Sandhu and Paul D. Varosy, https://doi.org/10.1093/eurheartj/ehac013.

Aims This study aims to estimate the cost-effectiveness of percutaneous left atrial appendage occlusion (LAAO) compared to standard stroke prevention care for patients with atrial fibrillation (AF) and contraindication to oral anticoagulation (OAC) in a Swedish healthcare and public sector perspective.

Methods and results We used a combined decision tree and cohort Markov model to estimate costs and quality-adjusted life-years (QALYs) over a lifetime horizon with LAAO compared to standard of care where the treatment effect is based on a recent meta-analysis. According to our analysis, LAAO gives more QALYs than standard of care (7.11 vs. 6.12). Furthermore, LAAO treatment is related to the first-year cost of 14 984 Euro (EUR) and higher average healthcare costs over the lifetime by about 4010 EUR, which gives an incremental cost-effectiveness ratio of LAAO vs. standard of care at 4047 EUR per gained QALY. From a public sector perspective, LAAO reduces average costs due to substantial reductions in long-term care and, thus, implies that LAAO is dominant from a public sector perspective (lower average costs and better health outcomes).

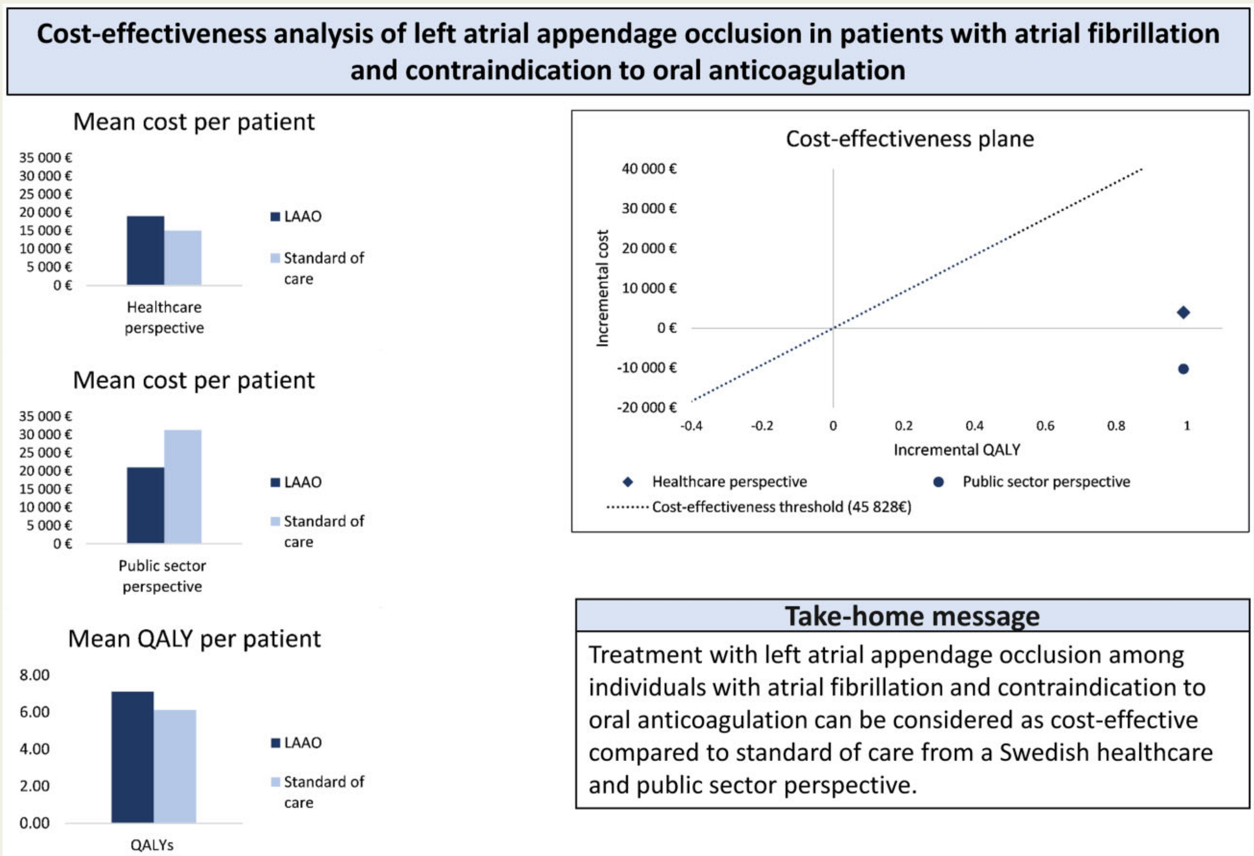
Conclusion From both Swedish healthcare and public sector perspectives, LAAO can be considered cost-effective compared to standard of care for individuals with AF and contraindication to OAC. However, these results must be confirmed in health economic evaluations alongside the ongoing randomized clinical trials.

Key Question Is left atrial appendage occlusion (LAAO) cost-effective for patients with atrial fibrillation (AF) and contraindication to oral anticoagulation (OAC) compared to the standard of care from a Swedish healthcare and public sector perspective?

Key Finding LAAO is associated with lower cost than the standard of care from a public sector perspective and an incremental cost of 4010 Euro from a healthcare perspective. Furthermore, LAAO is related to better health outcomes than the standard of care.

Take Home Message Treatment with LAAO among individuals with AF and contraindication to OAC can be considered as cost-effective compared to the standard of care from a Swedish healthcare and public sector perspective.

* Corresponding author. Tel: +46 733518446, Email: frida.labori@gu.se



Structured Graphical Abstract

Keywords Atrial fibrillation • Contraindication • Left atrial appendage occlusion • Left atrial appendage closure • Ischaemic stroke • Cost-effectiveness analysis

Introduction

Stroke is the second most common cause of death and the second largest cause of disability worldwide,[1] about 50% of all stroke survivors suffer from long-term disabilities.[2] Stroke can negatively impact health-related quality of life for stroke survivors for many years. The economic burden of stroke is extensive for both the individual and society. The total cost of stroke in the European Union (EU) was 45 billion in 2015, and around 1% of all EU healthcare spending was on stroke-related healthcare.[3] Out of the total costs for stroke, about half relate to formal healthcare costs, e.g. primary care, in-patient care, and medication. Furthermore, stroke is associated with high non-healthcare-related costs, including production loss due to mortality [5 billion Euro (EUR)], productivity loss due to morbidity (4 billion EUR), and informal care (16 billion EUR).[3] In Sweden, the estimated cost of stroke was ∼500 million EUR in 2009, of which 55% was related to inpatient care and 12% to municipal care such as home care services and special housing.[4]

Atrial fibrillation (AF) is prevalent in 3–4% of the global population,[5] and substantially increases the risk for the most common stroke type, ischaemic stroke. Prevention of ischaemic stroke using oral anticoagulation (OAC) is essential in AF (the term OAC is used for novel OAC and vitamin K antagonists). ESC guidelines for the diagnosis and management of AF developed in collaboration with the European Association for Cardio-Thoracic Surgery recommend OAC for AF patients with a CHA_2DS_2-VASc score of ≥2 for men and ≥3 for women.[5]

OAC effectively prevents ischaemic strokes among individuals with AF, but OAC is also associated with adverse events such as gastrointestinal bleeding or haemorrhagic stroke. Parts of the population with AF in need of stroke prevention are, therefore, ineligible for treatment with OAC due to contraindications such as bleeding, anaemia, or previous intracranial bleeding.[5] Instead, these patients can be recommended for left atrial appendage occlusion (LAAO) as stroke prevention.[5] Our study aims to assess the cost-effectiveness of LAAO for Swedish patients with AF and contraindication to OAC. The current literature on the cost-effectiveness of LAAO primarily focuses on patients with AF eligible for OAC and indicate that LAAO is cost-effective compared to both novel oral anticoagulants and vitamin K antagonists.[6,7] However, there is limited evidence on the cost-effectiveness of LAAO for individuals with AF and contraindication to OAC, i.e. the patient population that is recommended LAAO treatment in Europe. To our knowledge, the existing studies focusing on this population only consider a payer perspective and do not consider all stroke-related costs (e.g. for special housing and home care) from a public sector perspective and use treatment effect estimates from very small samples.[8,9] We address these limitations by considering a broader range of stroke-related costs and by leveraging a more precise effect estimate from a recent meta-analysis of 29 observational studies on the effectiveness of LAAO in patients with AF and contraindication to OAC.[10]

Methods

Due to the lack of randomized controlled trials (RCTs) focusing on individuals with AF, increased risk of ischaemic stroke and contraindication to OAC, we estimated the cost-effectiveness of LAAO compared to standard of care using decision-analytic modelling. We used a combined decision tree and Markov model, and our analyses are undertaking both Swedish healthcare and public sector perspectives. We illustrate the structures of the decision tree and Markov model in *Figure 1*.

Cohort

The hypothetical cohort used in the Markov model consists of patients with AF, increased risk of ischaemic stroke, and contraindication to OAC. When defining the risk of ischaemic stroke, we used the risk assessment tool CHA_2DS_2-VASc, which is defined by Congestive heart failure or left ventricular dysfunction (1 point), Hypertension (1 point), Age $\geq$75 (2 points), Diabetes (1 point), previous Stroke (2 points)-Vascular disease (1 point), Age 65–74 (1 point) and female Sex (1 point) (CHA_2DS_2-VASc). The average CHA_2DS_2-VASc in the cohort is 4 and age 74 years at the start of the model, which we based on the average CHA_2DS_2-VASc and age for the study population in a systematic review and meta-analysis.[10]

Left atrial appendage occlusion treatment

The treatment under investigation is percutaneous endocardial LAAO. Percutaneous endocardial LAAO is a procedure that closes the left atrial appendage with a medical device such as Watchman (Boston Scientific), Amplatzer Amulet (Abbott Medical), and LAmbre (Lifetech Scientific) to decrease the risk of ischaemic stroke. According to the ESC guidelines for AF,[5] LAAO can be a treatment alternative for stroke prevention in individuals with AF, increased risk of ischaemic stroke, and contraindication to OAC. In Sweden, the post-procedural treatment consists of aspirin for 6 months after the procedure (to decrease the risk of device-related thrombosis), followed by no pharmacological antithrombotic treatment.

Standard of care

In our analysis, we compared LAAO with standard of care in Sweden. Our analysis refers to standard of care as no pharmacological antithrombotic treatment to prevent ischaemic stroke in individuals with AF, increased risk of ischaemic stroke, and contraindications to OAC.[11] Therefore, aspirin is not considered a comparator in our analysis, following the ESC guidelines for AF,[5] which state that aspirin monotherapy (antiplatelet treatment) should not be used for stroke prevention in this patient population.

Model structure

During the intervention year (Year 1), we used a decision tree to allocate the cohort into the Markov model for LAAO, including patients with successful and unsuccessful LAAO procedures and the Markov model for the standard of care. Furthermore, we used the decision tree to estimate the first-year costs of LAAO treatment.

We used the Markov model to extrapolate the cost and health effects from the year after the intervention (Year 2) and forward. The model applies a one-year cycle length (i.e. individuals can change health state every year). The model used a lifetime horizon and continued until >99.9% of the individuals in a cohort entered the all-cause mortality health state.[12]

In the Markov model, we divided the health states related to ischaemic stroke according to the modified Rankin scale (mRS), which measure the individual's level of disability and dependency in daily life. The scale ranges from zero to six, where zero refers to no dependency and six is dead.[13]

The Markov model consists of 11 health states (*Figure 1*). During the second year, individuals can enter one of the following states: stroke-free survival, ischaemic stroke mRS 0–2 (no dependency), ischaemic stroke mRS 3 (moderate dependency), ischaemic stroke mRS 4–5 (severe dependency), or all-cause mortality. The stroke-free survival health state includes still alive individuals who have not yet had an ischaemic stroke. Individuals cannot return to this health state after entering any of the other health states. Each ischaemic stroke health state is related to a recurrent ischaemic stroke and post-ischaemic stroke health state. After an individual has had an ischaemic stroke, they can have an additional ischaemic stroke (recurrent stroke) with the same mRS status or a recurrent stroke with higher mRS. If the individual did not have stroke recurrence, the individual would enter a post-ischaemic stroke state with the corresponding mRS in the next cycle. An individual can only stay in any ischaemic stroke health states for one cycle before entering either the recurrent ischaemic stroke or the post-ischaemic stroke state. The individuals can remain in the health states 'recurrent ischaemic stroke' and 'post-ischaemic stroke' for an unlimited number of cycles. Individuals who have entered the post-ischaemic stroke states can have additional ischaemic strokes by entering any recurrent ischaemic stroke state. In the Markov model, the individuals cannot enter a health state with lower mRS (dependency in daily life) than in the previous cycle. The cohort can enter the all-cause mortality health state from all health states.

Transition probabilities

As illustrated in the decision tree (*Figure 1*), individuals with contraindications to OAC can be assigned LAAO or standard of care. The LAAO procedure can either be successful or unsuccessful. We assume that 97.3% have a successful procedure based on a recent systematic review and meta-analysis.[10] Individuals with a successful LAAO procedure continue to the Markov model with transition probabilities related to LAAO treatment in Year 2. In contrast, individuals with an unsuccessful LAAO procedure continue to the Markov model for LAAO treatment. However, they are assigned transition probabilities related to standard of care treatment. The cohort with the standard of care enters the Markov model with transition probabilities associated with the standard of care.

Risk of ischaemic stroke

Our model assumes that the risk of having an ischaemic stroke after LAAO treatment is 1.39 per 100 person-years, based on a meta-analysis that estimated the incidence rate of ischaemic stroke of patients with AF, contraindication to OAC and a CHA_2DS_2-VAS score of 4.[10] We based the distribution of mRS categories for individuals with LAAO treatment

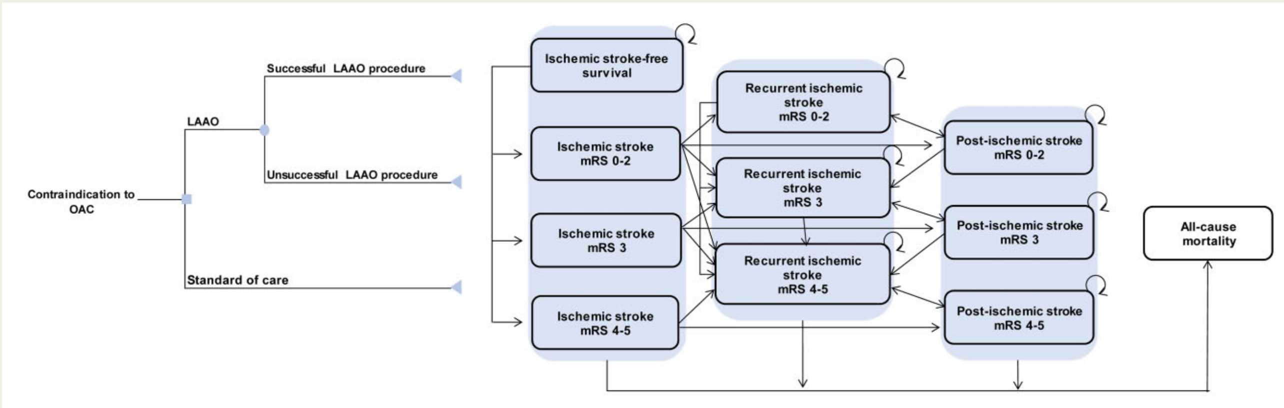


Figure 1 The decision-analytic model: decision tree used for Year 1 and the long-term Markov model for the remaining years.

on the distribution reported by Reddy *et al.*,[9] which suggests that individuals with an ischaemic stroke after LAAO treatment have fewer strokes that result in mRS 3 and mRS 4–5 compared to the individuals with standard of care in our analysis (*Table 1*). The assumed risk of ischaemic stroke for individuals with standard of care is 5.5 per 100 person-years, based on a predicted risk score estimated through a cohort with AF and no stroke prevention in Sweden.[14] We estimated the distribution of mRS categories when having an ischaemic stroke without stroke prevention in a dataset from the Swedish Stroke Register dataset (Riksstroke) (ethical approval: Dnr: 817_17 and Dnr: 2019-03535). The dataset includes individuals diagnosed with International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes *I.63 Cerebral infarction* and *I.64 Stroke, not specified as haemorrhage or infarction* in Year 2010 or 2011 in Sweden. The dataset includes individuals with age 64–84, a range that is 10 years younger and older than the mean age at the start of the model. The reason for this age span is to get a larger sample. We estimated the mRS distribution by mapping available variables in the Riksstroke dataset into mRS scores according to the article by Eriksson *et al.*[15] After experiencing an ischaemic stroke, all individuals in the model have a 5.1% annual risk of recurrent stroke.[16]

Table 1 Distribution of modified Rankin scale categories after ischaemic stroke with left atrial appendage occlusion treatment and standard of care

mRS category	LAAO treatment (proportion)	Standard of Care (proportion)
From mRS 0–2		
mRS 0–2	0.88	0.60
mRS 3	0.06	0.19
mRS 4–5	0.06	0.21
From mRS 3		
mRS 3	0.50	0.47
mRS 4–5	0.50	0.53
From mRS 4–5		
mRS 4–5	1	1

LAAO, left atrial appendage occlusion; mRS, modified Rankin scale.

Risk of death

We based age-related mortality on public-use data from Statistics Sweden[17] and the National Board of Health and Welfare.[18] Age-related mortality was divided into 5-year age categories and calculated by dividing the total number of deaths (except deaths due ICD-10 I.63 and I.64) by the population size in the corresponding age group. Age-related mortality applies to all health states in the Markov model. The yearly stroke-related risk of death is set to 23.3% and is a weighted average based on the population size of the percentage of individuals who died within a year after ischaemic stroke in the age groups 65–74 and 75–84.[19] The risk of stroke-related death was added to the age-related mortality in the health stages related to ischaemic stroke and recurrent stroke.

Resource use and cost

Left atrial appendage occlusion

We applied all costs related to the LAAO procedure in Year 1 of the model, including a pre-procedure cardiac computed tomography (CT), transthoracic echocardiography, a post-procedure physician visit, post-procedure cardiac CT, transoesophageal echocardiography, procedure cost, and related inpatient care. Individuals with a successful LAAO procedure have pharmaceutical treatment consisting of aspirin during the first six months.

Healthcare visits

Healthcare visits divide into inpatient care, specialized outpatient care and primary care. We based healthcare utilization on Lekander *et al.*,[20] who reports average resource use for the first and second years after an ischaemic stroke for each mRS category. We apply the resource use the first year after an ischaemic stroke in the health states 'ischaemic stroke' and 'recurrent stroke' and second-year resource use for the post-ischaemic stroke health state. Resource use in each health state is presented in Supplementary material online, *Table S1*.

Home care services and special housing

To estimate the additional cost of home care and special housing, we estimated the proportion of individuals who change their living arrangement and receive home care or move to special housing after an ischaemic stroke through the dataset from the Riksstroke data described in the *Risk of ischaemic stroke* section. For the individuals that change their living arrangement, i.e. receive home care services or move to special housing, we apply the average resource use based on the resource use reported

Table 2 Unit costs

Cost item	EUR	Statistical range* (EUR)	Reference
Health care			
Inpatient care[a] (day)	723	(578; 867)	20
Inpatient care[b] (day)	656	(525; 787)	20
Specialized outpatient care (visit)	167	(134; 201)	20
Primary care (visit)	109	(87; 131)	20
Municipal care			
Home care services (hour)	43	(34; 51)	22
Special housing (day)	224	(179; 269)	23
LAAO			
Cardiac CT (pre-procedure)	355	(284; 426)	Cost per patient
TTE (pre-procedure)	276	(220; 331)	Cost per patient
LAAO procedure	13 225	(10 580; 15 870)	Cost per patient
Physician visit (post-procedure)	347	(278; 416)	Cost per patient
TEE (post-procedure)	417	(334; 501)	Cost per patient
Cardiac CT (post-procedure)	355	(284; 426)	Cost per patient
Aspirin (6 months)	10	(8; 12)	21

CT, computed tomography; EUR, Euro; LAAO, left atrial appendage occlusion; TEE, transoesophageal echocardiography; TTE, transthoracic echocardiogram.
[a]The unit cost applied for inpatient care when entering the health states ischaemic stroke and recurrent stroke.
[b]The unit cost applied for inpatient care when entering the health state post-ischaemic stroke.
*Statistical range is ±20% from the base case value.

by Lekander *et al.*[20] (Supplementary material online, *Table S1*). Our Markov model assumes that individuals with mRS 0–2 have no additional home care services or special housing after an ischaemic stroke. We assume this because when mapping variables in the dataset from Riksstroke to mRS,[15] a criterion for mRS 0–2 is that individuals live in their own housing without home care services. Similarly, we assume that individuals with mRS 3 have no additional utilization for special housing. However, 49% of the individuals with mRS 3 have home care services after the ischaemic stroke. Individuals with mRS 4–5 can have either home care or special housing. Per the Riksstroke data, we assume that 21% and 40% have home care services and special housing, respectively. We apply home care and special housing during the first year in the health states ischaemic stroke and the second-year utilization in the post-ischaemic stroke health state.

Unit costs

The average procedure cost of LAAO is based on the medical episode when a device-related code registered at Sahlgrenska University Hospital (the largest hospital in Sweden located in Gothenburg). We received all costs related to the LAAO procedure from the cost per patient database at the Sahlgrenska University Hospital. The prices of pharmacological treatments were estimated using the Dental and Pharmaceutical Agency, product of the month (May 2021).[21] Unit cost applied for inpatient care, specialized outpatient care, and primary care are based on the unit costs reported by Lekander *et al.*[20] We based the unit cost for home care services on the average cost per hour of home care services in Sweden 2011,[22] and the cost of living in a special housing per day was based on the average yearly cost of special housing in Sweden in Year 2018[23] divided by 365. We report all unit costs in *Table 2*. Deaths (including those that were stroke-related) were not associated with any costs in our model due to a lack of relevant data (this is a conservative approach that favours the standard of care arm). All prices are presented in the year 2020 price level, and we applied a 3% discount rate. Costs are presented as EUR and are converted from Swedish krona (SEK) to EUR with an exchange rate of 10.91, i.e. 1 EUR = 10.91 SEK.

Health outcomes

Health outcomes are provided through quality-adjusted life-years (QALYs). We estimated the average decrements in QALY weight for each mRS category through the dataset from Riksstroke described in the *Risk of ischaemic stroke* section. The average QALY weight decrements were based on Ghatnekar *et al.*[24] Our dataset from Riksstroke does not contain the proxy response question, i.e. if healthcare personnel or relatives answered the questionnaire. Therefore, the coefficient for proxy responses was not applied. When calculating the QALY weights for each mRS category, we applied the QALY weight decrements to the EuroQol-5 dimensions index for age group 70–79 and 80–88 presented by Burström *et al.*[25] The age-related QALY weight for 70–79 was applied for age 74–79, and for ages ≥80, the QALY weight for 80–88 years was applied. The QALY decrements from stroke-free survival to each mRS category are reported in *Table 3*. We applied QALY weights when the cohort entered the Markov model, and no QALY weights were applied in the decision tree.

Perspective of the analysis

We carried out analyses from the Swedish healthcare perspective and the public sector perspective. The healthcare perspective included the costs that occur within the healthcare sector, such as inpatient care and primary care. In addition to healthcare costs, the public sector perspective also consists of municipal care costs, such as home care and special housing. We did not include the cost of production loss in either analysis because the cohort's age was 74 years at the start of the model. In the results, we present healthcare and public sector costs as the mean cost per patient during a lifetime horizon in each treatment alternative and the incremental cost (i.e. the difference in cost between the treatment alternatives). QALYs are presented as the mean number of QALYs per

Table 3 Age-related quality-adjusted life-year weights and quality-adjusted life-year decrements applied according to modified Rankin scale

Health state	QALY weight	95% confidence interval	Reference
Stroke-free survival age 70–79	0.790	(0.77, 0.81)	(25)
Stroke-free survival age ≥80	0.740	(0.70, 0.78)	(25)
mRS category	**QALY weight decrement**	**95% confidence interval**	**Reference**
mRS 0–2	0.097	(0.04, 0.16)	Riksstroke data
mRS 3	0.235	(0.18, 0.29)	Riksstroke data
mRS 4–5	0.707	(0.65, 0.77)	Riksstroke data

mRS modified Rankin scale; QALY, quality-adjusted life-year.

patient from a lifetime perspective and the incremental QALYs (i.e. the difference in QALYs between treatment alternatives). We present the base case cost-effectiveness result as an incremental cost-effectiveness ratio (ICER), which estimates the cost per QALY gained. To judge cost-effectiveness, we used the commonly used threshold value in Sweden of 500 000 SEK[26] (45 829 EUR).

Sensitivity analysis

We used both a one-way deterministic sensitivity analysis (DSA) and a probabilistic sensitivity analysis (PSA) to assess uncertainty in the cost-effectiveness results.

In the DSA, we changed one input parameter at a time keeping all others at base case value, and the input parameters were decreased and increased by 20%. The 10 parameters with the most significant influence on the ICER are illustrated in a Tornado diagram.

When conducting the PSA, we performed 1000 simulations, varying the input parameters within a range and applying different distributions. Standard errors were not available to the authors for any input parameters except for the risk of ischaemic stroke with LAAO treatment, QALY weights, and QALY decrements. Therefore, we calculated the standard error by assuming that a statistical range of ±20% around the base case value equals the confidence interval. We applied the gamma distribution to all unit costs, count input parameters and QALY decrements. We applied a beta distribution for input parameters with a restricted range between 0 and 1, such as the distribution of mRS categories after an ischaemic stroke. We present detailed information on the distribution applied to each input parameter in Supplementary material online, *Table S2*. We illustrate the results of the 1000 simulations and the base case ICER in a cost-effectiveness plane.

Scenario analysis

We performed several scenario analyses to address the different uncertainties in the base case analysis. In our base case analysis, LAAO reduces the risk of ischaemic stroke by 74.7% (treatment effect). It also reduces dependency in daily life (mRS) after an ischaemic stroke; a larger share of the stroke-affected individuals have mRS 0–2. We performed a scenario analysis where we only changed the treatment effect (incidence of ischaemic stroke with LAAO treatment) on ischaemic stroke to 50% and 25%. As a second scenario analysis, we conducted an analysis where we assumed LAAO treatment to have the same distribution of the mRS as the standard of care, i.e. LAAO does not affect dependency in daily life after an ischaemic stroke. Simultaneously, we reduced the treatment effect to 50%, 25%, and until the ICER was above the Swedish threshold value.

Table 4 Mean costs and health outcomes per patient from the Markov model

	LAAO	Standard of care	Difference
Costs			
Healthcare perspective	19 032 EUR	15 022 EUR	4010 EUR
Public sector perspective	21 029 EUR	31 281 EUR	-10 252 EUR
Health outcomes			
QALYs	7.11	6.12	0.99

EUR, Euro; LAAO, left atrial appendage occlusion; QALY, quality-adjusted life-year.

Results

Costs

In our analysis, LAAO treatment is associated with a first-year cost of 14 984 EUR, including a procedure cost, clinical examinations, physician visit, and post-procedural treatment. Moreover, LAAO is associated with lower cost during the remaining years compared to standard of care. From a healthcare perspective, the average cost per patient is estimated to be 19 032 EUR and 15 022 EUR for LAAO and standard of care, respectively, i.e. an incremental cost with LAAO of 4010 EUR. From the public sector perspective, the mean cost per patient over the lifetime perspective was estimated to be 21 029 EUR with LAAO and 31 281 EUR with standard of care, which suggest that LAAO treatments cost 10 252 EUR less than standard of care from the public sector perspective. All costs are presented in *Table 4*.

Health outcomes

In our model, LAAO is related to higher average QALYs per patient over the lifetime perspective compared to standard of care. The main drivers of this difference are that LAAO is associated with a lower risk of having the first ischaemic stroke in our model. In addition, the individuals that experience ischaemic stroke get less disabling ischaemic stroke than individuals with standard of care. The mean estimated QALY per patient with LAAO is 7.11 and 6.12 with

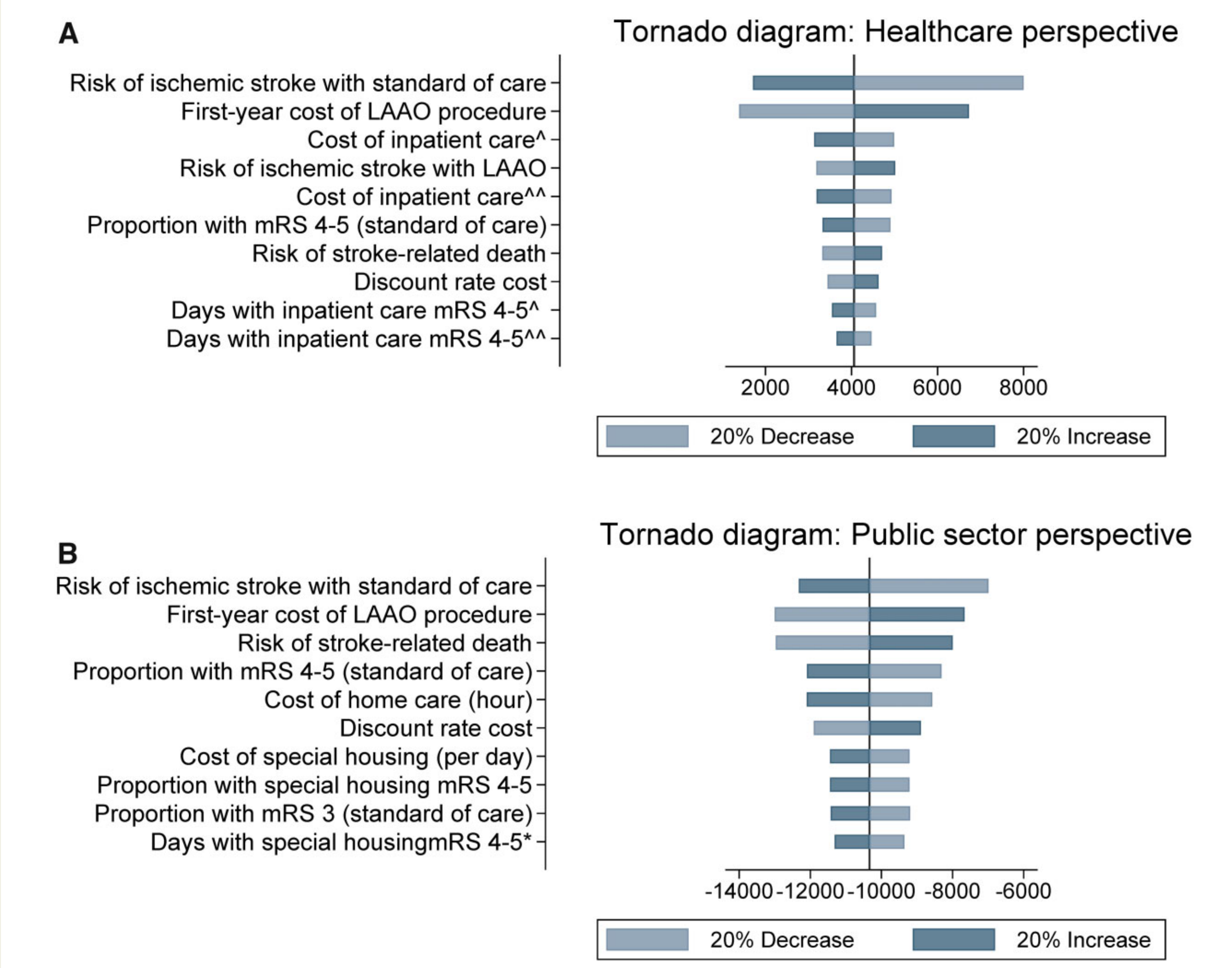


Figure 2 Tornado diagram from the deterministic sensitivity analysis from both the healthcare perspective (*A*) and the public sector perspective (*B*). ^Applied for inpatient care when entering the health states ischaemic stroke and recurrent stroke. ^ ^Applied for inpatient care when entering the health state post-ischaemic stroke. *Applied for special housing when entering the health state post-ischaemic stroke.

standard of care over the lifetime perspective, which results in an incremental QALY of 0.99 (*Table 4*).

Cost-effectiveness analysis

According to our model, stroke prevention with LAAO is more costly and more effective from a healthcare perspective, with an ICER of 4047 EUR, which is below the Swedish threshold value of 45 829 EUR. From a public sector perspective, stroke prevention with LAAO is dominant, i.e. less costly and more effective than standard of care (*Table 4*).

Deterministic sensitivity analysis

The input parameter that has the greatest impact on the base case ICER from a healthcare perspective is the predicted risk of ischaemic stroke with standard of care, followed by the cost of the LAAO procedure. Similarly, from the public sector perspective, the predicted risk of ischaemic stroke with standard of care was the input parameter with the largest impact on the ICER. We report the ten most influential input parameters from the healthcare and public sector perspectives in *Figure 2*. However, when conducting the DSA regardless of perspective, none of the changes in input parameters influences the interpretation of the base case results, and according to the DSA, the base case results can therefore be considered robust.

Probabilistic sensitivity analysis

Of the simulated ICER, most are still in the northeast quadrant of the cost-effectiveness plane (i.e. more costly, more effective) and locates below the Swedish threshold value (*Figure 3A*) from a healthcare perspective. However, some of the simulated ICERs from a health care perspective is located in the southeast quadrant. From a public sector perspective, 99.9% of the ICERs remain located in the southeast quadrant in the cost-effectiveness plane from a public sector perspective (i.e. less costly, more effective) (*Figure 3B*).

Scenario analysis

When we decrease the treatment effect, i.e. reducing the incidence rate of ischaemic stroke with LAAO to 50% and 25%, the ICERs from the healthcare perspective remain below the Swedish threshold

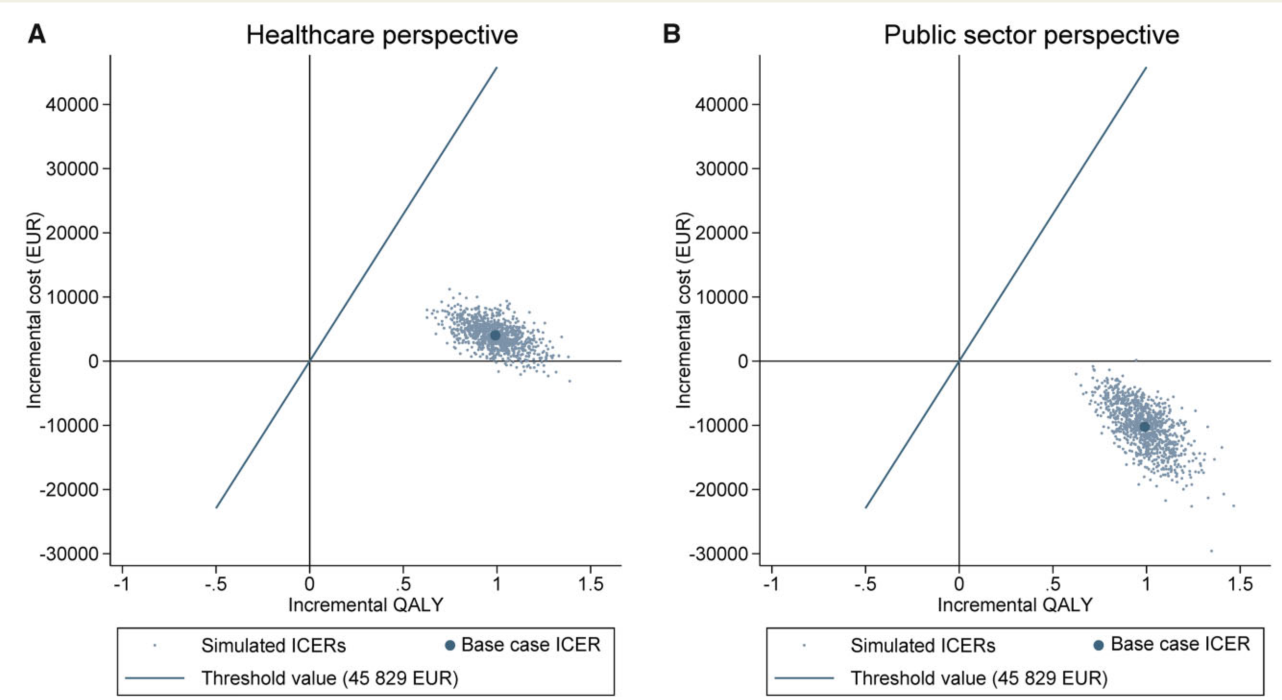


Figure 3 Cost-effectiveness plane illustrating the base case incremental cost-effectiveness ratio together with the simulated incremental cost-effectiveness ratios from a healthcare perspective (*A*) and a public sector perspective (*B*).

value. From a public sector perspective, LAAO is still dominant compared to standard of care. In the final scenario analysis, we assume similar distribution of mRS categories as the standard of care and reduce the treatment effect. When we reduce the treatment effect of LAAO on ischaemic stroke to 50%, LAAO is considered cost-effective. However, when we reduce the treatment effect to 25%, the ICER is located above the threshold value, i.e. not considered cost-effective from a healthcare perspective. When we reduce the treatment effect of LAAO on ischaemic stroke to 50% and 25%, the ICERs from the public sector perspective remains below the threshold value. From a public sector perspective, the treatment effect can be reduced to 20% before the ICER exceed the threshold value. Detailed results from the scenario analysis are available in Supplementary material online, *Table S3*.

Discussion

Our analysis indicates that preventing ischaemic stroke with LAAO in individuals with AF, increased the risk of ischaemic stroke and contraindication to OAC is cost-effective both from a healthcare perspective and a public sector perspective. LAAO is associated with the first-year cost of 14 984 EUR. From a healthcare perspective, LAAO is associated with a higher cost of 4010 EUR per patient over the lifetime horizon than standard of care. However, LAAO is cost saving from a public sector perspective. LAAO is also associated with more QALYs than standard of care over a lifetime horizon (*Graphical Abstract*).

Our results are coherent with the two other studies investigating the cost-effectiveness of LAAO as stroke prevention in individuals with AF and contraindication to OAC.[8,9] However, our analysis differs from these studies in several ways. Previous studies[8,9] focusing on individuals with contraindications compared LAAO treatment with aspirin. According to the ESC guidelines for AF, monotherapy with aspirin is considered non-effective for stroke prevention and for older populations with AF, this treatment can even be harmful. Therefore we compared LAAO with standard of care, which in our case equals no pharmacological antithrombotic treatment since there is no effective pharmacological antithrombotic treatment for AF patients with contraindication to OAC.

Furthermore, we estimated the costs that appear within the healthcare budget and a broader public sector perspective, including home care services and special housing, which, to our knowledge, none of the other cost-effectiveness analyses of LAAO has included.

In addition, previous cost-effectiveness analyses of LAAO based the effectiveness of LAAO for stroke prevention on small sample sizes. Saw *et al.*[8] based the clinical input of LAAO on 52 individuals[27], and Reddy *et al.*[9] used 150 individuals[28] to estimate the clinical inputs related to LAAO. In contrast, we based the effectiveness of LAAO for stroke prevention (treatment effect) on a systematic review and meta-analysis that included 7519 individuals with AF and contraindication to OAC that had received LAAO treatment.

We did not consider it appropriate to use the treatment effects from the PROTECT-AF and/or PREVAIL trials[29,30] since these RCTs compared LAAO to vitamin K antagonists in populations eligible for OAC. However, ongoing RCTs (e.g. ASAP-TOO, NCT02928497) focus on individuals with AF and contraindication to OAC, but these are not yet completed. Thus, until the effectiveness of LAAO is documented in one or more well-conducted RCTs, including the relevant population given the European guidelines, the actual effectiveness of LAAO contains significant uncertainties.

An uncertainty that could affect cost-effectiveness is that we assume that individuals with LAAO treatment experience ischaemic strokes that are less disabling (lower mRS). Due to the lack of other sources, we make this assumption based on the study by Reddy *et al.*[9] that presents the mRS distribution in the PROTECT-AF population. However, as mentioned above, their study population differed from the population we investigated.

We accounted for the uncertainties above in the scenario analysis by setting the mRS distribution for both alternatives to the standard of care mRS distribution and simultaneously reduced the treatment effect. As a result, the scenario analysis showed that the treatment effect (reducing ischaemic strokes) of LAAO could be lowered to 20% and remained below the threshold value from a public sector perspective (base case treatment effect 74.7%).

Limitations

A common concern when applying different sources of secondary data to populate a decision-analytic model is how well the secondary data are matched to the patient population in the model. We have addressed this as far as possible by thoroughly reviewing potential data sources and applied the sources that we consider to be most appropriate for our patient population and our model. Further, we have conducted a PSA where all input values are varied simultaneously.

Due to the lack of completed RCTs focusing on individuals with AF and contraindication to OAC, we based the effectiveness of LAAO on a systematic review and meta-analysis that included 29 observational studies and 7951 individuals with contraindications to OAC and mean CHA_2DS_2-VASc of 4.32 that received LAAO.[10] In that study, the authors compared the estimated incidence rate of ischaemic stroke at CHA_2DS_2-VASc 4 with LAAO to no antithrombotic treatment via a predicted risk score. The predicted risk score was based on a large cohort of individuals with AF in Sweden.[14] This comparison could potentially overestimate the effectiveness of LAAO, so we, in addition to the DSA and PSA, also conducted several scenario analyses where we reduced the treatment effect from 74.7% to 50%, 25%, and until LAAO treatment was no longer considered cost-effective. Our scenario analyses indicated that LAAO could be cost-effective if the treatment effects are at least 20%, which could be used as a benchmark when future randomized evidence is produced.

Another limitation is the assumptions made when conducting the PSA. Uncertainty estimates were unavailable for most input parameters. For these parameters, we assumed a statistical range of ±20% from the base case value, as ignoring the uncertainty completely is not considered a viable option.[31] If we had access to actual standard errors for all parameters, the PSA results would potentially be more accurate.

A final limitation is that we did not consider the increased risk of major bleeding during the first six months after the LAAO procedure when the individual was on aspirin. Previous studies have shown that aspirin is associated with a significantly increased risk of major bleedings, with an absolute risk of 1.3% per year with aspirin.[32] However, since aspirin is prescribed only for six months after the LAAO procedure, the increased risk of major bleeding for half a cycle in the model would have a limited impact on the results. Major bleeding was, therefore, not included in the model.

Conclusions

According to our decision-analytic model, LAAO is cost-effective for stroke prevention in individuals with AF and contraindication to OAC from both a healthcare perspective and a public sector perspective. However, our results need to be confirmed by health economic evaluations alongside the currently ongoing clinical trials that directly evaluate LAAO in this patient group. In the meantime, this study contributes with valuable information for decision-makers about the cost-effectiveness of LAAO for individuals recommended LAAO treatment for stroke prevention.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Acknowledgements

All authors have contributed to the conceptualization of the study and the Markov model. Data collection and analysis were performed by Frida Labori, which also wrote the first draft of the manuscript. However, all authors after that commented and reviewed previous versions of the manuscript. All authors approved the final version of the article.

Funding

The authors were not awarded any funding for the submitted work.

Conflict of interest: K.J. has received grants for clinical stroke research from the Swedish state under the agreement between the Swedish government and the county councils, the ALF agreement, which have been paid to the institution. F.L., J.P., C.B., and M.S. have no conflicts of interest to declare.

Data availability

The majority of the input data in the analyses is available in the article or the supplementary material. Input data that are not available in the article or the supplementary material can be shared upon request to the corresponding author.

References

1. GBD 2016 Stroke Collaborators. Global, regional, and national burden of stroke, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2019;**18**:439–458.
2. Donkor ES. Stroke in the 21(st) century: a snapshot of the burden, epidemiology, and quality of life. *Stroke Res Treat* 2018;**2018**:3238165.
3. Wilkins E, Wilson L, Wickramasinghe K *et al. European Cardiovascular Disease Statistics, 2017 Edition*. Brussels, Belgium: European Heart Network; 2017.
4. Ghatnekar O, Steen Carlsson K. Kostnader för injuknande i stroke år 2009. En incidensbaserad studie; 2012. p38.
5. Hindricks G, Potpara T, Dagres N *et al.* ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2021;**42**:373–498.
6. Reddy VY, Akehurst RL, Amorosi SL, Gavaghan MB, Hertz DS, Holmes DR Jr. Cost-effectiveness of left atrial appendage closure with the WATCHMAN

device compared with warfarin or non-vitamin K antagonist oral anticoagulants for secondary prevention in nonvalvular atrial fibrillation. *Stroke* 2018;**49**: 1464–1470.
7. Reddy VY, Akehurst RL, Gavaghan MB, Amorosi SL, Holmes DR Jr. Cost-effectiveness of left atrial appendage closure for stroke reduction in atrial fibrillation: analysis of pooled, 5-year, long-term data. *J Am Heart Assoc* 2019;**8**:e011577.
8. Saw J, Bennell MC, Singh SM, Wijeysundera HC. Cost-effectiveness of left atrial appendage closure for stroke prevention in atrial fibrillation patients with contraindications to anticoagulation. *Can J Cardiol* 2016;**32**:1355.e9-1355–e14.
9. Reddy VY, Akehurst RL, Armstrong SO *et al.* Cost effectiveness of left atrial appendage closure with the Watchman device for atrial fibrillation patients with absolute contraindications to warfarin. *Europace* 2016;**18**:979–986.
10. 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. *J Interv Card Electrophysiol* 2021;**61**:215–225.
11. The National Board of Health and Welfare. Nationella riktlinjer för hjärtsjukvård-Stöd för styrning och ledning; 2018. p94.
12. Siebert U, Alagoz O, Bayoumi AM *et al.*; ISPOR-SMDM Modeling Good Research Practices Task Force. State-transition modeling: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force—3. *Value Health* 2012;**15**: 812–820.
13. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988;**19**: 604–607.
14. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. *Eur Heart J* 2012;**33**:1500–1510.
15. Eriksson M, Appelros P, Norrving B, Terént A, Stegmayr B. Assessment of functional outcome in a national quality register for acute stroke: can simple self-reported items be transformed into the modified Rankin Scale? *Stroke* 2007;**38**: 1384–1386.
16. Amarenco P, Lavallée PC, Labreuche J *et al.*; TIAregistry.org Investigators. One-year risk of stroke after transient ischemic attack or minor stroke. *N Engl J Med* 2016;**374**:1533–1542.
17. Statistikdatabasen. Folkmängden efter region, civilstånd, ålder och kön. År 1968; 2019. https://www.statistikdatabasen.scb.se/pxweb/sv/ssd/START__BE__BE0101__BE0101A/BefolkningNy/ (17 February 2021).
18. The National Board of Health and Welfare. Statistics on Cause of Death; 2019. https://www.socialstyrelsen.se/statistik-och-data/statistik/statistikamnen/dodsorsaker/ (4 May 2021).
19. Rosengren A, Giang KW, Lappas G, Jern C, Torén K, Björck L. Twenty-four-year trends in the incidence of ischemic stroke in Sweden from 1987 to 2010. *Stroke* 2013;**44**:2388–2393.
20. Lekander I, Willers C, von Euler M *et al.* Relationship between functional disability and costs one and two years post stroke. *PLoS One* 2017;**12**:e0174861.
21. Dental and Pharmaceutical Agency. *Product of the Month*. https://www.tlv.se/apotek/utbyte-av-lakemedel-pa-apotek/periodens-varor.html (4 May 2021).
22. Sveriges Komuner och Landsting. Kostnad per brukare- Jämförelser mellan kommuner inom omsorg om äldre och personer med funktionsnedsättning – utfall 2011; 2012. p44. https://webbutik.skr.se/bilder/artiklar/pdf/7164-843-3.pdf?issuusl=ignore (17 February 2021).
23. Kolada. Kostnad särskilt boende äldreomsorg, kr/brukare. https://www.kolada.se/verktyg/fri-sokning/?kpis=76370&years=30197,30196,30195&municipals=82304&rows=municipal,kpi&visualization=bar-chart (17 February 2021).
24. Ghatnekar O, Eriksson M, Glader EL. Mapping health outcome measures from a stroke registry to EQ-5D weights. *Health Qual Life Outcomes* 2013;**11**:34.
25. Burström K, Johannesson M, Diderichsen F. Swedish population health-related quality of life results using the EQ-5D. *Qual Life Res* 2001;**10**:621–635.
26. The National Board of Health and Welfare. Nationella riktlinjer för sjukdomsförebyggande metoder 2011- Hälsoekonomiskt underlag (bilaga); 2011. p48.
27. Urena M, Rodes-Cabau J, Freixa X, Saw J *et al.* Percutaneous left atrial appendage closure with the AMPLATZER cardiac plug device in patients with nonvalvular atrial fibrillation and contraindications to anticoagulation therapy. *J Am Coll Cardiol* 2013;**62**:96–102.
28. Reddy VY, Mobius-Winkler S, Miller MA *et al.* Left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation: the ASAP study (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology). *J Am Coll Cardiol* 2013;**61**:2551–2556.
29. Holmes DR, Reddy VY, Turi ZG *et al.*; PROTECT AF Investigators. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet* 2009;**374**:534–542.
30. Holmes DR Jr, Kar S, Price MJ *et al.* Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure Device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. *J Am Coll Cardiol* 2014; **64**:1–12.
31. Briggs AH, Weinstein MC, Fenwick EA, Karnon J, Sculpher MJ, Paltiel AD; ISPOR-SMDM Modeling Good Research Practices Task Force. Model parameter estimation and uncertainty: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force—6. *Value Health* 2012;**15**:835–842.
32. Connolly SJ, Pogue J, Hart RG *et al.* Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med* 2009;**360**:2066–2078.