Cost Effectiveness of different treatment strategies for Non-valvular Atrial Fibrillation in patients after Intracerebral Hemorrhage

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Abstract

Background- Patients who survive an intracerebral hemorrhage (ICH) and suffer from non-valvular atrial fibrillation (NVAF) have an increased risk of both ischemic stroke and recurrent ICH. Currently there are different treatment options for these patients; vitamin K antagonists (VKA), non-vitamin K anticoagulation (NOAC), left atrial appendage occlusion (LAAO) or no treatment at all. We determined the most cost-effective option. ***Methods-*** We used a Markov model to evaluate quality of adjusted life years (QALY), additional costs and the incremental cost effectiveness ratio (ICER) of VKAs, NOACs and LAAO in comparison with no treatment, separately for 14 risk groups. The risk groups are independent of the treatment option and were classified based on the CHA_2DS_2-VASC (low, medium, high risk of ischemic stroke) and the HAS-BLED (low, medium, high risk of ICH) score. Also location of the previous ICH was taken into account (lobar vs non-lobar), since lobar ICH has a higher recurrence rate. ***Results-*** All treatment options resulted in health gain: in the base case no treatment resulted in 4.2 QALYs, VKA in 7.0 QALYs, NOAC in 7.4 QALYs and LAAO in 8.4 QALYs gained. NOAC was slightly more favorable than VKA treatment, in terms of cost-effectiveness. But every risk group LAAO was the most cost-effective treatment. In the risk group with lowest expected risks (Ischemic stroke low, ICH low, non-lobar) the ICER of LAAO was 31,878 €/QALY, compared to no treatment. In the risk group with highest expected risks (Ischemic stroke high, ICH high, lobar) the ICER was 31,785 €/QALY, compared to no treatment. The ICER of LAAO increases with expected risk until the ischemic stroke medium, ICH medium, non-lobar risk group with an ICER of 33,641 €/QALY. ***Conclusion-*** LAAO is the most cost effective treatment in NVAF patients who survive ICH and results in most QALYs gained.

Introduction

In 2016 there were 42,700 new cases of stroke in the Netherlands, of which 19,100 cases in the age category 75 years and older.[1] Approximately 4,270 to 6,405 of the stroke cases are intracerebral hemorrhages (ICHs). 39% to 44% of the ICHs are related to the use of antithrombotic drugs and 10% to 24% to the use of oral anticoagulation. Non-valvular atrial fibrillation (NVAF) is the primary indication for oral anticoagulation in 72% to 79% of the ICH cases related to oral anticoagulation.[2]

From the given numbers there can be concluded that in patients who suffered from ICH, often have NVAF as well. Patients who survive an ICH and suffer from NVAF have increased risk

of ischemic stroke[3-6] and recurrent ICH. To prevent ischemic stroke in patients with NVAF, anticoagulation is typically prescribed. Vitamin K Antagonists (VKA) are very effective in reducing the risk of stroke with risk reductions up to 64-68%[7,8]. However, anticoagulation also increases this risk of recurrent ICH in patients after a first ICH[9,10]. As multiple treatment options exist, a current clinical dilemma concerns assessing what treatment, if any, the patient is likely to benefit most from.

In 2003 a decision model was published to support treatment decisions in this context. This decision model contained three different treatment strategies: anticoagulation with Warfarin, anticoagulation with aspirin, or no anticoagulation. In patients with lobar ICH, withholding anticoagulation improved health outcomes by 1.9 Quality-Adjusted Life Years (QALYs, one QALY equals one life year in perfect health). For patients with deep hemispheric ICH, health outcomes improved by 0.3 QALYs.[11] No treatment was found to be more effective than anticoagulation.

Over the last years new treatment options for NVAF have become available that may carry a lower risk of ICH than the classic VKA. Non-vitamin K Oral Anticoagulants (NOACs) were found to be non-inferior to VKAs and reduce the risk of ICH recurrence with 19%[12,13]. The European guidelines, therefore, favor the use of NOACs over the use of VKAs in treatment of NVAF[12]. In addition to medical treatment of NVAF, there is also an invasive treatment available: Left Atrial Appendage Occlusion (LAAO). With this treatment, a little pouch in the left atrium is closed, resulting in blood clots being formed to a lesser degree or not at all. This means that the patient eventually does not have to take anticoagulation, in the first 6 months anticoagulation is prescribed to prevent thrombus from forming on the device. The downside of this treatment is that it is an invasive treatment and complications can occur. Also the costs of the LAAO are considerably higher in comparison with VKAs and NOACs.[14]

When it comes to treatment reimbursement, in many countries the treatment costs are considered next to health benefits. The costs of the different treatments vary greatly, LAAO costs approximately 50 times more than VKAs and 16 times more than NOACs[14-16]; however the VKA and NOAC costs are yearly recurring costs while LAAO is a one-off price. Which of the treatments is more cost-effective over a lifetime is unclear.

The objective of our study is therefore to assess which NVAF treatment option is most cost-effective to allow more informed decision making in NVAF patients following ICH.

Methods

To structure this study we used the CHEERS guideline of the ISPOR Task Force [17].

Target population and subgroups based on risk

The base-case population are patients who survived an ICH and suffer from NVAF. The characteristics of these patients are based on a recent article that describes three clinical trials with ICH patients. The mean age of the base-case population is 73 years old and 58% are men. Overall 38% had a lobar ICH and 62% a deep located ICH.[18]

We defined the different health states based on the modified Rankin Scale (mRS, appendix A). Only patients in good condition after the first ICH were included in the base-case population, 'good condition' is defined as a mRS score of 0 to 2. There is only sparse literature on the distribution of patients over the mRS scores after a second event [10,19]. In this study a mRS score of 0 to 3 was used as definition of the health state 'Reasonable good condition' after a second event[20]. A 'Poor condition' after a second event equals a mRS score of 4 or 5, with a score of 6 equal to 'Death'. [21]

In the base-case population patients have different risks of a recurrent ICH or an ischemic stroke, due to risk factors other than previous ICH and NVAF. Therefore, we created several subgroups (Table 1 and 2). These risk groups are important in the model, because, according to literature, the ICH and ischemic stroke risks likely have considerable influence on the effect of the investigated treatment options. The risk groups are based on the CHA_2DS_2-VASc and the HAS-BLED (see appendix A). The HAS-BLED was not developed for risk prediction after ICH. However, a recent study found that the HAS-BLED could also be useful to assess the risk of major bleeding after a spontaneous ICH. The sensitivity and specificity were 79.1% and 29.2%, respectively, with a C-statistic of 0.54 (0.50-0.59).[22] Despite the relatively low C-statistic, the HAS-BLED provides the most accurate predicted risk of bleeding compared to other scores[23]. The HAS-BLED scores of 0-1, 2 and ≥3 are used to define the low, medium and high ICH risk groups. The CHA_2DS_2-VASc is a validated instrument to assess the risk of ischemic stroke[24]. However, the CHA_2DS_2-VASc has not been validated for ischemic stroke risk assessment after ICH. Nonetheless, this scoring method is increasingly being used for this purpose and is the best predictive method currently available[25]. The CHA_2DS_2-VASc scores of 0-3, 4-6 and 7-9 are used for define the low, medium and high ischemic stroke risk groups. All risk groups with corresponding ICH and ischemic stroke incidence rates are shown in table 1.

After a first ICH the risk of recurrence is quite unclear and according to the literature ranges from 0 to 24% per year, based on 1 to 16 years of follow-up[26]. Commonly known risk factors for recurrence are hypertension, location of the previous ICH, advanced age and cerebral amyloid angiopathy[2,9,26-30], see Appendix A. The target group also has a substantial risk of ischemic stroke, due to NVAF. The known risk factors for ischemic stroke are advanced age, hypertension, prior TIA or stroke and diabetes[25,31-34]. Because of the overlap in risk factors for ICH and ischemic stroke[26,30,35], the combinations of a high risk of ischemic stroke (ICH) with a low risk of ICH (ischemic stroke) are excluded from the analysis.

Furthermore, the risk groups were divided according to a lobar or non-lobar (deep) location of the first ICH because lobar ICH (often related to cerebral amyloid angiopathy) has a higher rate of recurrence than non-lobar ICH (often related to hypertensive small vessel disease)[26,28]. Approximately 38% of the first ICHs are lobar. Of all the recurrent ICHs about 57% of the patients previously had a lobar ICH. [18] The HAS-BLED and CHA_2DS_2-VASc do not account for the location of the bleeding[22,25]. In table 2 the HAS-BLED and CHA_2DS_2-VASc scores are combined with

location of previous ICH in to 14 risk groups. Risk group 1 has the lowest expected risk and risk group 14 has the highest expected risk.

Table 1 Chances of ICH and ischemic stroke according to the HAS-BLED and CHA_2DS_2-VASc score.

ICH	**HAS-BLED**	Risk of a major bleeding in patients with VKA without previous ICH [24]	**Ischemic Stroke**	**CHA_2DS_2-VASc**	Risk of ischemic stroke in patients with AF after ICH[25]
Low	0-1	0.6%	Low	0-3	4.5%
Medium	2	1.6%	Medium	4-6	10.1%
High	≥3	2.6%	High	7-9	23.1%

Table 2 Risk groups

			ICH					
			Low		Medium		High	
			HAS-BLED 0-1		HAS-BLED 2		HAS-BLED ≥3	
			Non-Lobar	Lobar	Non-Lobar	Lobar	Non-Lobar	Lobar
Ischemic stroke	Low	CHA_2DS_2-VASc 1	1	2	3	4		
	Medium	CHA_2DS_2-VASc 5	5	6	7	8	9	10
	High	CHA_2DS_2-VASc 8			11	12	13	14

Comparators

In this study 4 different treatment strategies are compared: VKA, NOAC, LAAO and no treatment. Historically, VKA was the most commonly administered treatment to patients with NVAF, but in recent years NOACs have gained popularity. A 2013 study showed that NOACs are at least non-inferior to VKAs[12]. The guidelines state that these medication options are clinically equally effective.[36] Thus, in most developed countries the share of the (old) standard treatment VKA is currently decreasing and the share of the (new) standard treatment NOAC is increasing.

Aside from medical treatment Left Atrial Appendage Occlusion (LAAO) is an upcoming treatment for NVAF. There is increasing evidence that LAAO is effective in preventing ischemic stroke in NVAF patients[37]. Last, there are claims that no treatment is the most effective management strategy in some cases[11,38]. For this reason and because the discussion which treatment is currently the 'golden standard', 'no treatment' is used as the reference treatment to compare the other treatment options with.

Besides the 4 mentioned treatment options, antiplatelet therapy is often mentioned in literature[39-44]. However, antiplatelets were proven to be not as effective as the VKAs and the NOACs[45-47]and therefore we did not include this therapy in our analysis.

Study perspective, Setting, Discount rate, Time horizon and Health outcomes

The Dutch guideline for health economic evaluations was followed for our study, and discount rates applied were 4% for costs and 1,5% for effects. The time horizon used is the lifetime time horizon. The primary health outcomes are expressed in Quality-Adjusted Life Years (QALYs), reflecting both quality and length of life. The guideline recommends to use a societal perspective, the literature found did not cover all societal costs and benefits, so healthcare perspective is used.[48]

Model and Assumptions

We developed A Markov cohort model , with which the clinical pathway of different cohorts of hypothetical patients was simulated. For LAAO specific health states were included, as opposed to drug treatment LAAO is an invasive treatment. The health states 'LAAO' and 'Complications' are specific to the LAAO strategy, the pathways for patients in the health state 'ICH NVAF Good Condition (stable after LAAO)' are identical for all strategies (see figure 1).

Some assumptions were necessary to simplify the model. The estimates of the transition probabilities were (if possible) based on long-term effects, to reflect the lifetime time horizon. However, these transition probabilities were then set constant, that is, do not change over time. Furthermore, it was assumed that after a second event no (new) treatment will be started, given that typically the condition of the patient will be very poor. No further events are modelled, as it is assumed that a 3rd event would always be fatal. After health state 'Poor' and 'Reasonable good condition' there is only the option to stay in that condition or die, from ICH, from ischemic stroke, or from other causes.

Model inputs and Assumptions

Evidence on transition probabilities, utilities and costs, was obtained from literature, and the resulting estimates can be found in table 3. Scopus was used to search for literature, cost-effectiveness studies and large clinical cohorts particularly were of interest. The description of population of every study used can be found in the appendices B and C.

The studies used for estimating the risks of recurrent ICH/ischemic stroke mostly use a target population who suffered oral anticoagulation related ICH. Since our target group has NVAF, it is plausible that a part of the target group has suffered an ICH related to anticoagulation, therefore these studies are also used to obtain the probabilities, along with the studies with spontaneous ICH as start point.

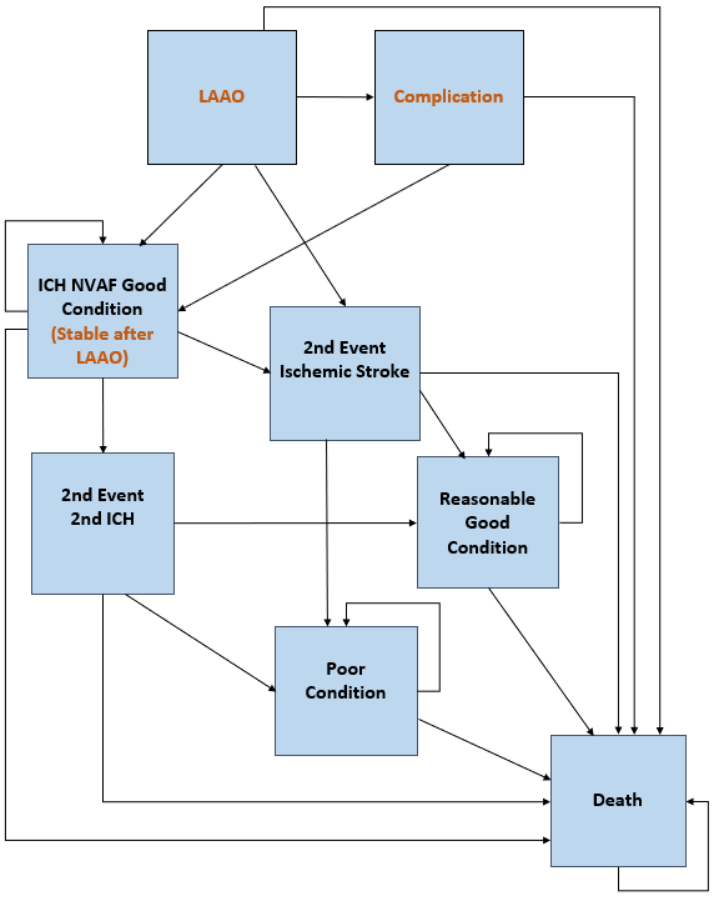


Figure 1 Markov model

The estimates for the risk reduction of ischemic stroke for VKAs and NOACs are based Warfarin and Apixaban. Differences in clinical benefits between the different medications in a single category was assumed to be negligible[20]. In the VKAs category Warfarin was chosen, since most found studies concerning VKA included Warfarin. In the NOACs category, Apixaban was chosen because this is the best performer in terms of hemorrhage and ischemic stroke reduction. Only Dabigatran 150mg was performing better, but because of a higher risk of bleeding with increased age, 150mg would have to be switched to 110mg above 80 years old. In some groups the switch from 75 years and above is recommended.[16] In the base case population, as described in 'The target population and subgroups', Apixaban performs better due to advanced age.

For LAAO, estimates of complication risks and procedure related mortality risks were only available in patient groups without previous ICH. In our patient group these risks are therefore likely slightly higher than mentioned in recent studies[49,50]. The transition probability of death after complications has been adjusted with the help of an expert, the numbers of events are raised to reflect reality. In the studies above no deaths occurred, to estimate LAAO mortality more accurately it was assumed, that LAAO mortality was the same as the mortality with Percutaneous Coronary Intervention.

In the first 6 months of LAAO anticoagulation is prescribed. These effects (costs and risk on ischemic stroke and ICH) are included in the estimates found.

For patients in the health state 'Reasonable good condition' the long term utility of moderate stroke sequel is used, assuming that a second event always results in a decrease in utility. Furthermore, it is expected that patients in the health state 'Poor condition' have a lower utility than those in the health state 'Reasonable good condition'. Therefore, the utility observed in patients surviving Severe Stroke is used. [51]

In two studies by Sullivan (2005, 2006), the utility values of patients experiencing one of three complications of LAAO are given. For pericardial effusion an utility decrement of 0.048 was given, for device embolization an utility decrement of 0.120 and for major bleeding an decrement of 0.181 was given[52,53]. To estimate the utility of the complications, the utility decrements of different complications were combined, after uncertainty was processed.[52,53]

Table 3 Transition Probabilities

Transition probabilities					
From Health state	**To Health state**	**Value**	**Range**	**Distribution**	**Source**
LAAO	Complication	0.095	0.07-0.12	Beta	[49]
	2nd event ischemic stroke	0.011	0.00-0.02	Beta	[49]
	Death	0.012	0.01-0.01	Beta	[54]
Complication	Death	0.004	0.00-0.01	Beta	[49]
Stable	2nd event ICH	0.002	0.00-0.00	Beta	[50]
	2nd event ischemic stroke	0.016	0.01-0.02	Beta	[50]
	Death	0.030	0.02-0.04	Beta	[49]
ICH NVAF Good condition	2nd event ICH (NT)	0.013	0.01-0.02	Beta	[9]
	2nd event ischemic stroke (NT)	0.023	0.02-0.03	Beta	[55]
	Death (NT)	0.191	0.16-0.22	Beta	[56]
	2nd event ICH (VKA)	1.10*	0.96-1.16	Lognormal	[18]
	2nd event ischemic stroke (VKA)	0.46*	0.30-0.77	Lognormal	[18]
	Death (VKA)	0.32*	0.02-0.53	Lognormal	[18]
	2nd event ICH (NOAC)	0.42*	0.11-0.77	Lognormal	[16]

	2nd event ischemic stroke (NOAC)	0.92*	0.80-1.23	Lognormal	[16]
	Death (NOAC)	0.89*	0.81-1.05	Lognormal	[16]
2nd Event 2nd ICH	Reasonable good condition (mRS 0-3)	0.60	0.59-0.60	Dirichlet	[10]
	Poor condition (mRS 4-5)	0.15	0.14-0.15	Dirichlet	[10]
	Death	0.25	0.24-0.25	Dirichlet	[10]
2nd Event Ischemic Stroke	Reasonable good condition (mRS 0-3)	0.67	0.63-0.72	Dirichlet	[19]
	Poor condition (mRS 4-5)	0.18	0.15-0.22	Dirichlet	[19]
	Death	0.15	0.11-0.18	Dirichlet	[19]
Poor condition (mRS 4-5)	Death	0.22	0.15-0.28	Beta	[57]
Reasonable good condition (mRS 0-3)	Death	0.08	0.06-0.09	Beta	[57]
Utilities					
	NVAF ICH Good condition	0.86	0.80-0.92	Beta	[58]
	LAAO	0.06**	-0.01-0.14	Beta	[59,60]
	Complications	0.11**	0.08-0.13	Beta	[49,52,53]
	Stable	0.86	0.80-0.92	Beta	[58]
	2nd event ICH	0.14**	0.12-0.16	Beta	[53]
	2nd event Ischemic Stroke	0.14**	0.12-0.16	Beta	[53]
	Reasonably Good condition	0.60	0.52-0.68	Beta	[51]
	Poor condition	0.45	0.31-0.60	Beta	[51]
Costs					
	NVAF ICH Good condition (mRS 0-2)	€40,544		Gamma	[61]
	2nd Event Ischemic Stroke	€31,230		Gamma	[62]

	2nd Event ICH	€31,230		Gamma	62
	Reasonably Good condition (mRS 0-3)	€60,114		Gamma	61
	Poor condition (mRS 4-5)	€179,679		Gamma	61
	Death (mRS 6)	€56,430		Gamma	61
	Warfarin (VKA)	€125		Gamma	16
	INR monitoring costs	€143		Gamma	15
	Apixaban (NOAC)	€818		Gamma	63
	LAAO	€13,107		Gamma	14
	Complications	€14,665		Gamma	64
	Stable	€40,544		Gamma	61

* Hazard Ratios

** Disutilities

Costs and Resources

The costs used in the model were based on a literature search. Costs are updated to 2017 with Dutch inflation indices, one study needed to be converted to euros first (€1=$1.37; July 2014). In table 3 the costs estimates are shown. 7 out of 12 studies take direct and indirect costs into account. For a more detailed description of the costs and articles, see appendix C.

Analysis

The model outcome was in the form of an Incremental Cost-Effectiveness Ratio (ICER). In order to take uncertainty in the input parameters (evidence used) into account the ICER is based on probabilistic sensitivity analysis. Here, 1,000 samples of parameter values are drawn using Monte Carlo simulation, to determine the uncertainty in model outcomes. First the ICER of de treatments without the risk groups are calculated. Second, the ICER for every risk group included in the analysis in every treatment is calculated.

A one-way sensitivity analysis was conducted, where individual parameter values were increased and decreased by 20%. The impact of these changes per parameter on the ICER are shown in a tornado diagram. The one-way sensitivity analysis is only conducted on the Base Case ICER.

Errors were found in the model, which was determined shortly before the submission of the thesis. There was no time left to adjust the results. This will be corrected after submission, with the aim of writing an article.

Results

Incremental costs and outcome

The QALYs gained in the LAAO treatment is 4.2 against 2.8 QALY (VKA) and 3.2 QALY (NOAC), in comparison with no treatment. Table 4 show the incremental cost effectiveness ratios for VKA, NOAC and LAAO in comparison with no treatment. The ICERs of the treatments show that LAAO is most cost effective, with a cost of 28,307 €/QALY gained. In table 5 the ICERs are given per risk group for each treatment. LAAO is the most cost effective treatment in all risk groups, with ICERS between 31,785 €/QALY and 33,641 €/QALY. For VKA the ICERs ranged from 46,674 €/QALY to 65,150 €/QALY across risk groups. NOAC differed only slightly from VKA with ICERs from 45,471 €/QALY to 64,827 €/QALY. In appendix D incremental costs and QALYs can be found of all risk groups.

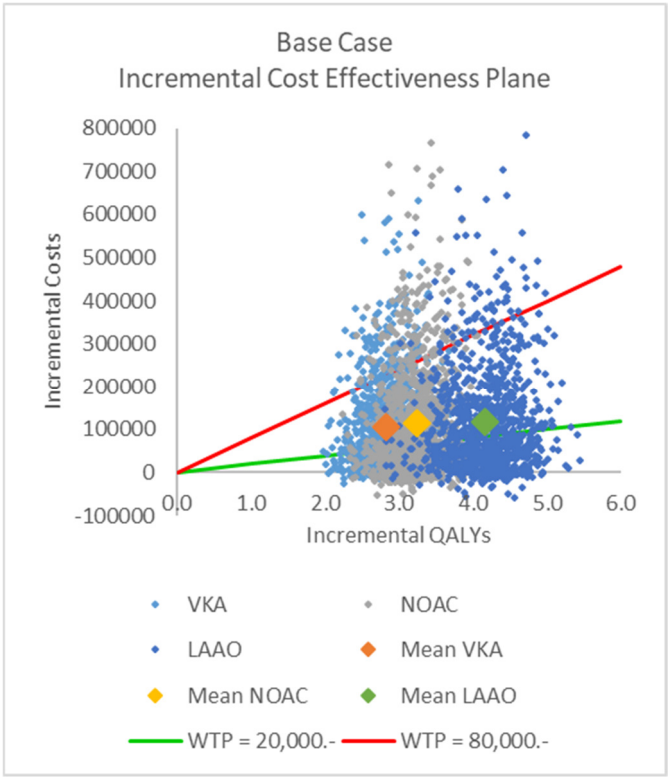
Table 4 ICERs Base Case

	No Treatment	**VKA**	**NOAC**	**LAAO**
Costs (€)	247,569	352,301	362,914	365,548
QALYs	4.2	7.0	7.4	8.4
Incremental Costs (€)	-	104,732	115,345	117,979
Incremental QALYs	-	2.8	3.2	4.2
ICER (€/QALY)		37,069	35,618	28,307

Table 5 ICERs VKA, NOAC and LAAO

ICER (€/QALY) VKA		**ICH**					
		Low		**Medium**		**High**	
		Non-Lobar	**Lobar**	**Non-Lobar**	**Lobar**	**Non-Lobar**	**Lobar**
Ischemic Stroke	**Low**	46,674	48,180	47,852	49,306		
	Medium	54,263	55,404	55,159	56,259	56,029	57,071
	High			63,884	64,597	64,472	65,150
ICER (€/QALY) NOAC		**ICH**					
		Low		**Medium**		**High**	
		Non-Lobar	**Lobar**	**Non-Lobar**	**Lobar**	**Non-Lobar**	**Lobar**
Ischemic Stroke	**Low**	45,471	47,042	46,696	48,216		
	Medium	53,408	54,610	54,348	55,507	55,263	56,363
	High			63,477	64,238	64,103	64,827

ICER (€/QALY) LAAO		ICH					
		Low		Medium		High	
		Non-Lobar	Lobar	Non-Lobar	Lobar	Non-Lobar	Lobar
Ischemic Stroke	Low	31,878	32,206	32,179	32,450		
	Medium	33,616	33,596	33,641	33,582	33,608	33,506
	High			32,416	32,060	32,157	31,785



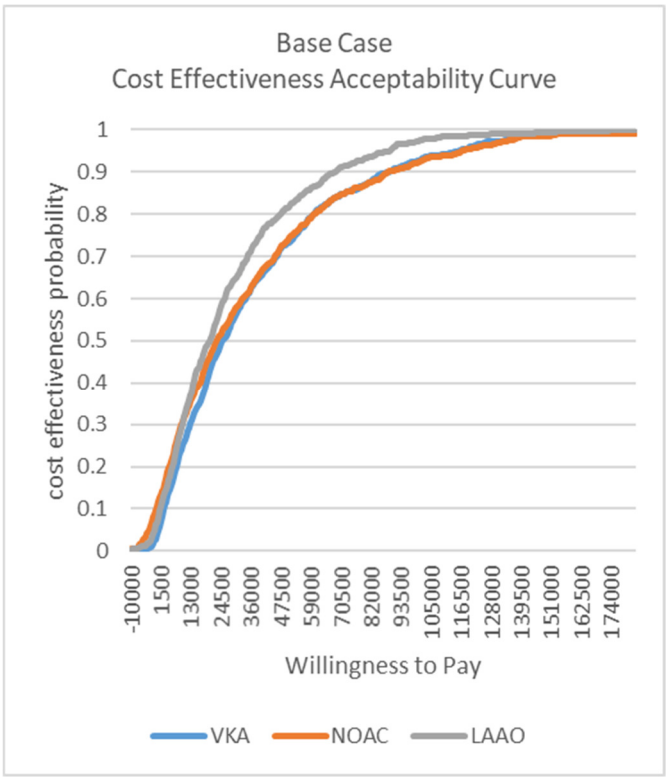


Figure 2

In figure 2 the incremental cost effectiveness plane and the cost effectiveness acceptability curve (CEAC) of the base case is shown, also the willingness to pay thresholds of €20,000.- and €80,000.- are included. Also the incremental cost effectiveness plane of the risk group with the lowest expected risk (low risk of ischemic stroke, Low risk of ICH and non-lobar location) and the highest expected risk (high risk of ischemic stroke, high risk of ICH and lobar location), are displayed in figure 3 and 4, respectively. In the ICER plane there is a great amount of overlap shown, in uncertainty of the treatments. For the three groups with results in Figure 2-4, also an cost effective acceptability curve is given. Notice that when de risk of both ischemic stroke and ICH increases, the curve of VKA and NOAC flattens and the curve of LAAO steepens in the CEACs (see figure 2, 3 and 4).

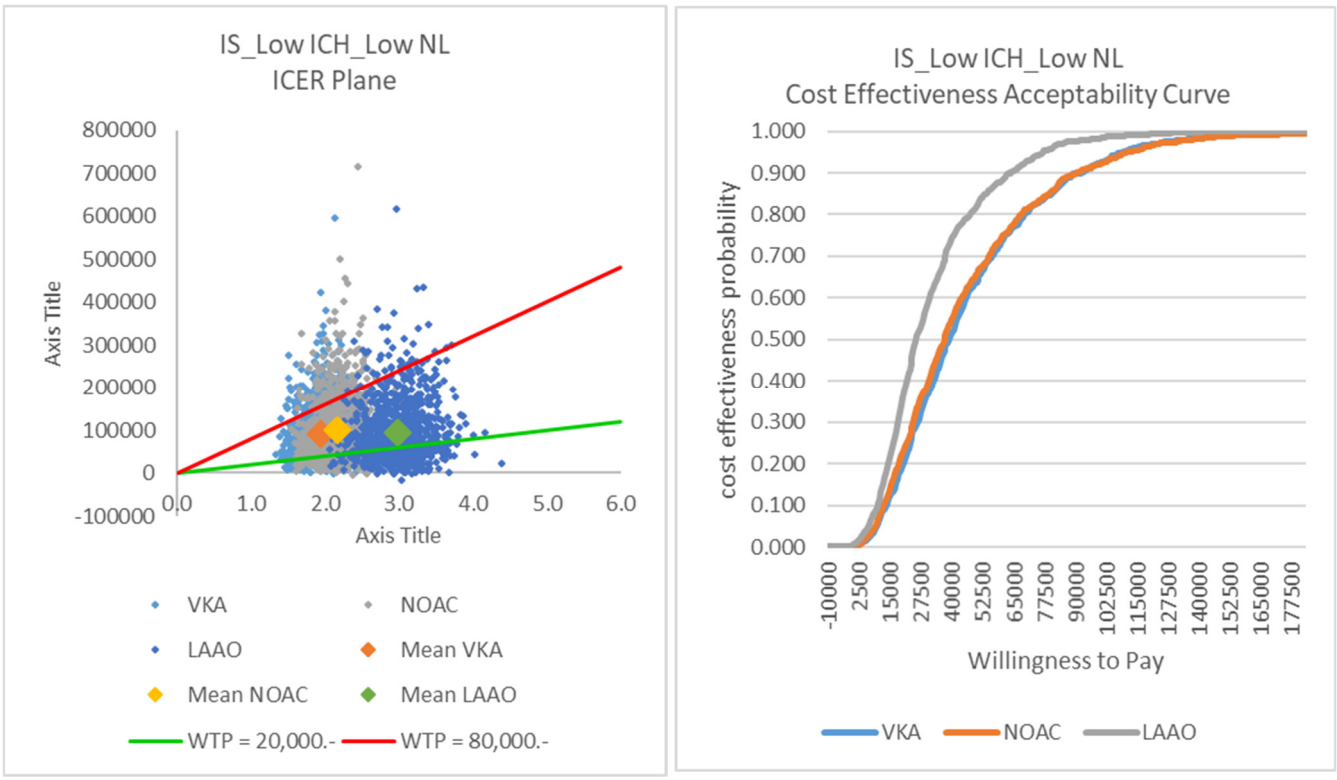


Figure 3

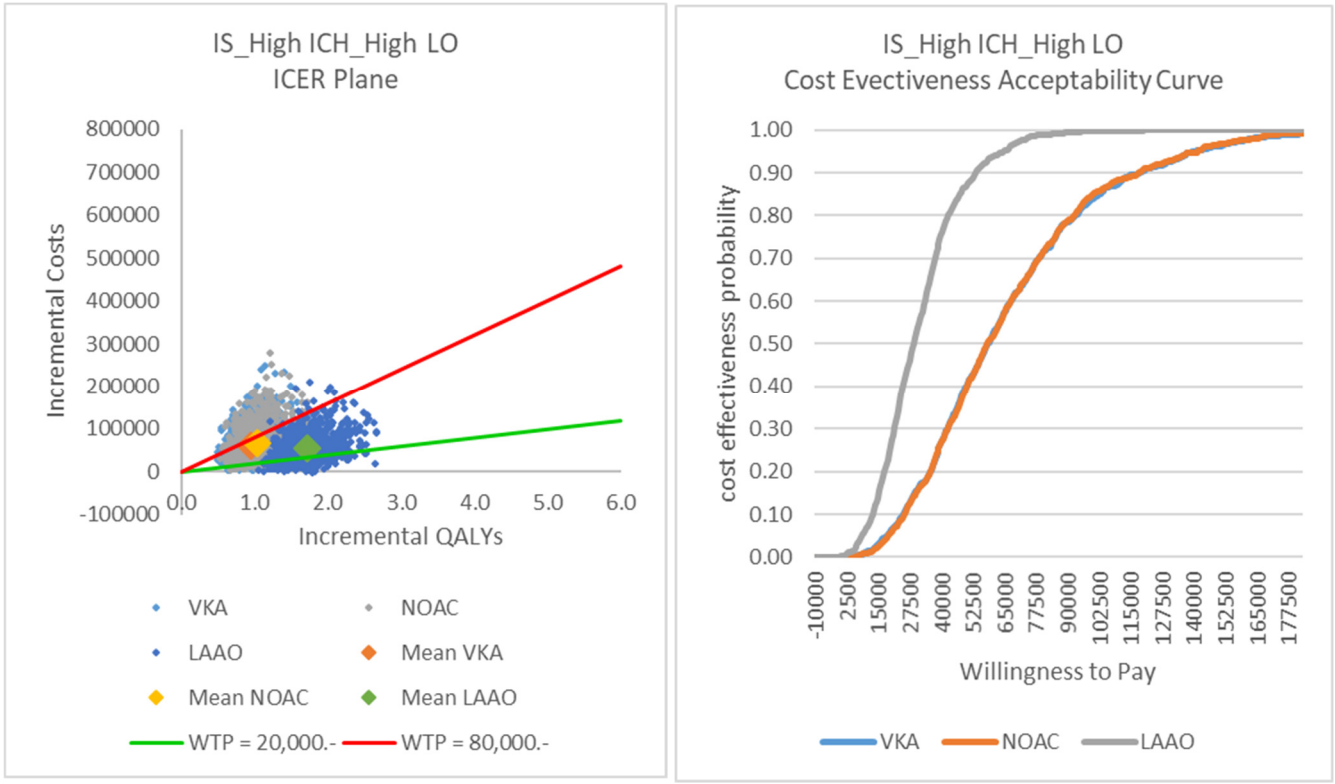


Figure 4

Characterizing uncertainty

One way analysis are conducted. Tornado plots are shown in figure 5, 6 and 7 these are the parameters per treatment which had the biggest influence on the base case ICER. Tornado plots of all other parameters are found in appendix E. Especially the parameters which influence health state 'good condition or stable' have a great impact on the ICER.

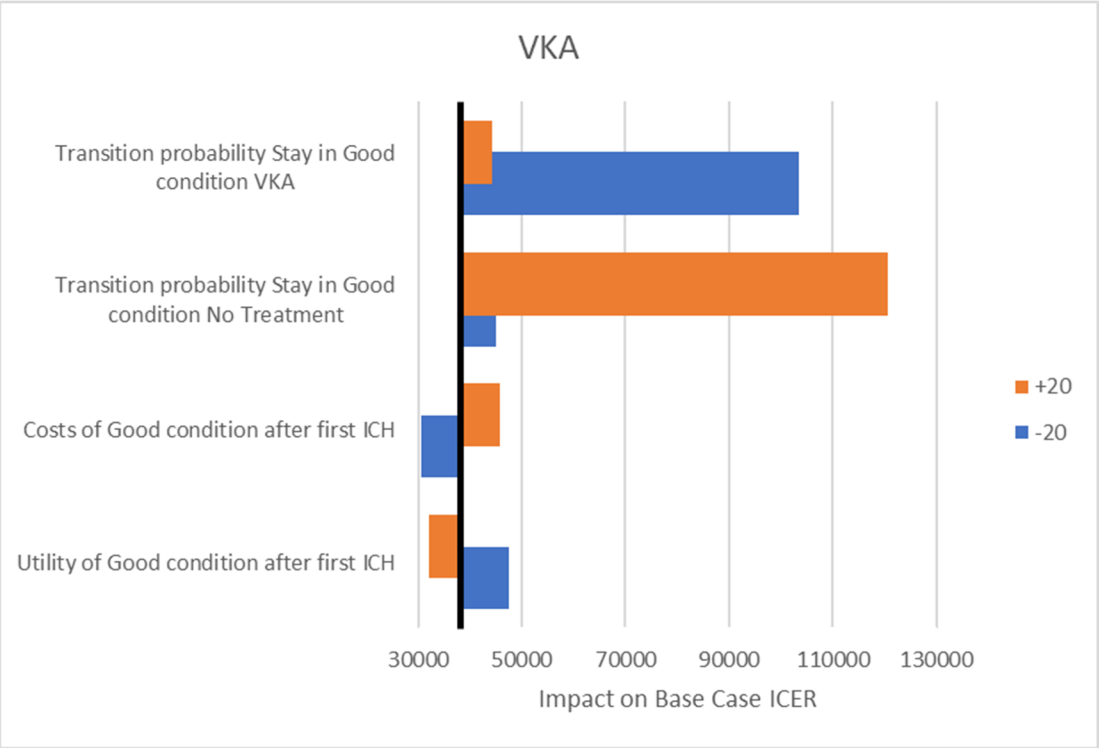


Figure 5

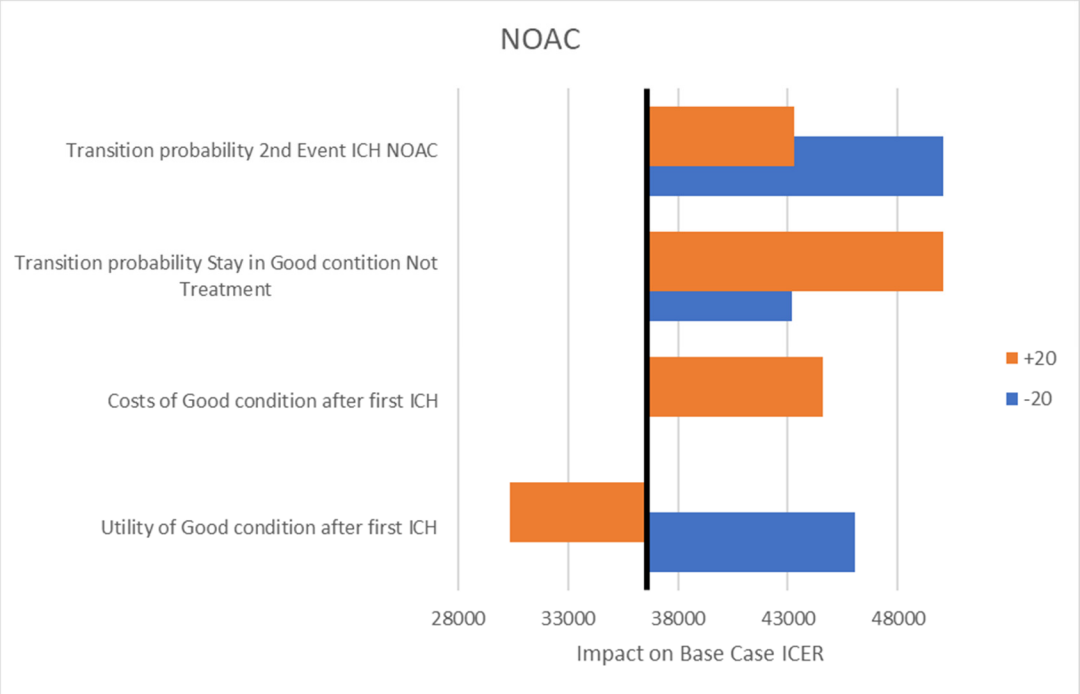
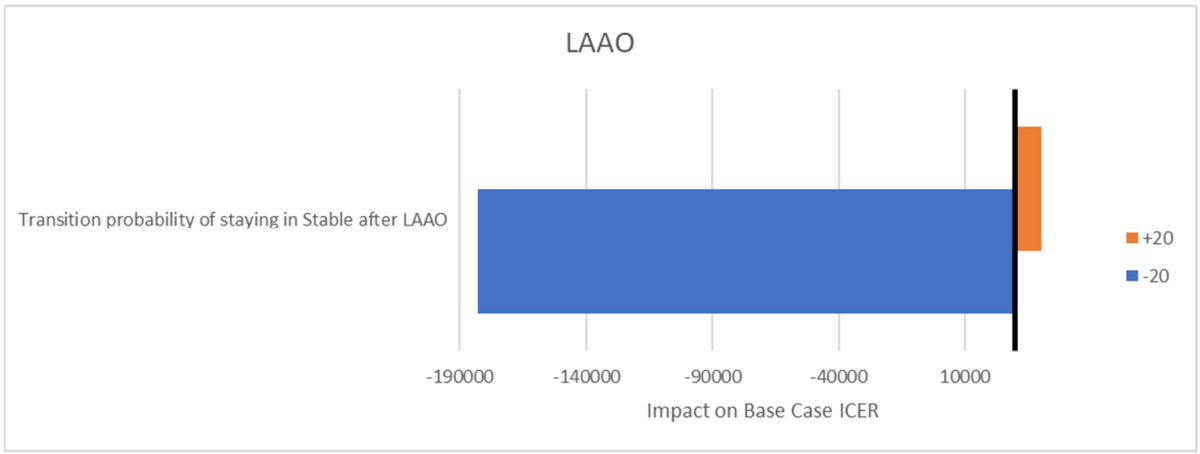


Figure 6



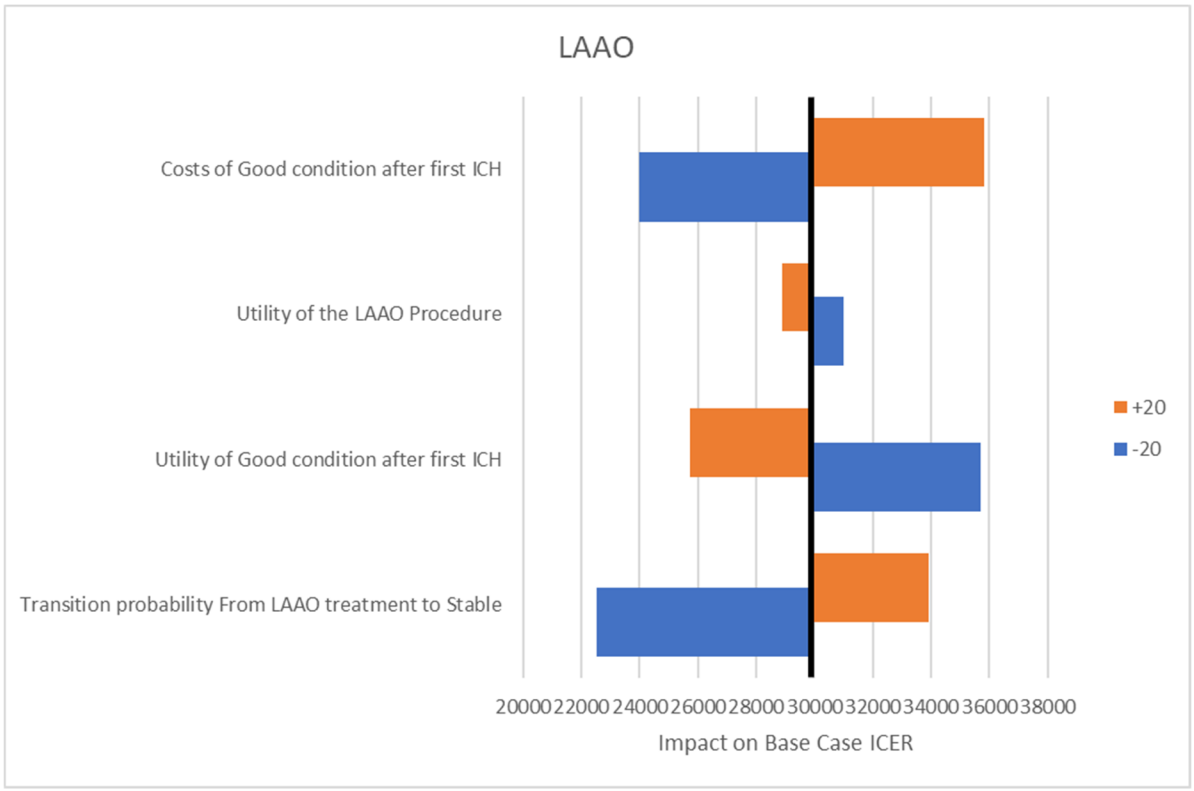


Figure 7

The transition probability of Staying in stable condition after LAAO had to be displayed in an other figure due to the big impact the parameter had on the Base Case ICER. Minus 20% on the probability to stay in health state 'Stable' gives a ICER of -182747, the incremental costs are -56342,75 and the incremental QALYs 0,31.

Heterogeneity

The differences in the group have been overcome by categorizing the risk groups. Differences in ICER between de risk groups are not large, except for the risk groups divided by Low, Medium and High risk of ischemic stroke. The groups with high risk of ischemic stroke have the largest ICER (€63,884 up to €65,150 for the VKA and €63,477 to 64,827 for the NOAC), except in the LAAO

treatment group, here the medium risk group of ischemic stroke has the largest ICER (€33,506 to €33,641). These numbers are shown in table 5. The difference in ICER between lobar and non-lobar location is small, approximately 1000 Euros per QALY gained. The ischemic stroke low risk, ICH low risk with non-lobar location of the previous ICH was expected to be the group with the lowest risk of an event and therefore to have the lowest ICER. This is not the case in the LAAO group.

Discussion

In all risk groups of ICH patients with NVAF LAAO was the most cost effective treatment strategy. All treatments resulted in QALY gains in comparison with no treatment. In the NOAC and VKA strategies the relationship between the expected level of risk and the ICER was more as expected (the group with the lowest expected risk also had the lowest ICER). In the LAAO risk groups this was not the case. In the last weeks there was concluded that mistakes were present in de model. These are not yet adjusted. Wrong results lead to wrong conclusions, read the results with caution.

Limitations

Our analysis had certain limitations. The transition probabilities for LAAO were based on a study population without an previous ICH. Thus these probabilities may be too optimistic, and consequently the benefits of LAAO over the other treatments may be overestimated. However, the clinical trial used was one of the first trials to carry out this procedure. Later study demonstrated a learning curve and reported lower complication risks[65]. This may have led to an underestimation of LAAO benefits, and a mitigation of the previously mentioned overestimation.

In clinical practice decisions on treatment are also based on specific patient characteristics. For example, caution is necessary when administering NAOCs to frail elderly, patients with impaired renal function and patients with possible poor adherence.[36] These risk factors are not included in the model.

In the model age-related mortality risks are combined with mortality risks for ischemic stroke and ICH, while the latter are already included in the former. Due to this overlap the total mortality risk is slightly overestimated.

The study is based on a healthcare perspective. According to the Dutch guidelines for economic evaluations in healthcare a societal perspective should be applied. The studies found to estimate the costs, unfortunately, did not all include the indirect costs, see appendix C. So, healthcare perspective is chosen.

Generalizability

Given the wide availability of VKAs, NOACs and LAAO procedures our results may also be of interest to countries other than the Netherlands. The Dutch costs and effects included in this model

can easily be adjusted. Generalization to non-western countries, however, may not be possible, given the known differences in (recurrent) ICH risks between Asian and western populations[66].

Current knowledge

Clinicians often take an well-educated gues what is the best treatment, if they have to choose whether to give a ICH patient and with NVAF anticoagulation[20]. The CHA_2DS_2-VASc and the HAS-BLED are helpful tools to asses risk of ischemic stroke and ICH in patients, but these are not validated on patients with a previous ICH. In previous studies different recommendations are given. One study published in 2003 recommended to withhold anticoagulation from the patients with previous lobar ICH, and that for all patients was best to avoid anticoagulation[11]. In a systematic review it is mentioned that patients may benefit from anticoagulation, but it remains unclear when medication should be started after ICH[2]. Furthermore, the cost-effectiveness of NOACs compared to VKAs in patients with NVAF has been studied[16], unfortunately these studies did not include patients with a history of ICH. Other studies assessed the risk of restarting anticoagulation in patients who suffered from ICH[6,38], but excluded NOACs. Regarding LAAO, a fairly new treatment for NVAF patients, nothing is known about cost effectiveness of the treatment. In Canada in 2016 a study is conducted, patients who suffered from ICH underwent LAAO and found safe[67]. This study is not used in the model since the research population was very small and therefore the resulting estimates contain substantial uncertainty. Missing is the cost effectiveness of the treatment. Our study contributes to close the knowledge gap in the situation outlined just now.

Our results corroborate previous research demonstrating that NOACs are cost effective and yield better health outcomes in comparison with VKA. However, LAAO outperforms both medication options in terms of health outcomes, and, even though it is more expensive, is the most cost-effective option of the four considered strategies. Given the limited evidence currently available on LAAO, further empirical research on this procedure is warranted, especially on long term outcomes in patients with previous ICH, and results may be useful in improving the robustness of the results from this cost-effectiveness analysis.

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Appendix A Definitions

Table a1 modified Rankin Scale (mRS)[21]

Grade	mRS
0	No symptoms at all
1	No significant disability: despite symptoms able to carry out all usual duties an activities
2	Slight disability: unable to perform all previous activities but able to look after own affairs without assistance
3	Moderate disability: requiring some help but able to walk without assistance
4	Moderately severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability: bedridden, incontinent and requiring constant nursing care and attention.
6	Death

HAS-BLED

Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (age >65 years), Drugs/alcohol concomitantly. For every risk factor present, one point is granted.[22]

0 to 9 points can be assigned, the score of 0-1 is a low score, 2 is a mediate score and 3 or higher is a high score.[24]

CHA_2DS_2-VASc

The CHA_2DS_2-VASc score assigns 2 points each for age 75 years or older and prior stroke or transient ischemic attack. It assigns 1 point each for hypertension, diabetes, peripheral vascular disease, age 65–74 years, and female gender[25].

0 to 9 points can be assigned, the score of 0-2 is a low score, 2-5 is a mediate score, 5 or higher is a high score.

Risk factors ischemic stroke and ICH[2,9,25-34]

Only for ischemic stroke	For both ischemic stroke and ICH	Only for recurrent ICH
Abnormal LV function	Hypertension	Lobar location first ICH
Diabetes mellitus	Advanced age	Cerebral amyloid angiopathy
Female gender	Prior stroke (ischemic or hemorrhagic)	Labile INR
Congestive heart failure	Abnormal renal/liver function	
Peripheral vascular disease	Drugs alcohol concomitantly	

Appendix B Utilities and Transition probabilities with population description

Transition probabilities and utilities with description of population used in the studies

Table a2 Transition Probabilities

From Health state	To Health state	Value	Range	Distribution	Study population	Male	Mean age	Country	Total Population	Source
LAAO	Complication	0.095		Beta	Patients with NVAF without previous ICH	70%	72	USA and Europe	707	[49]
	2nd event Ischemic Stroke	0.011		Beta	Patients with NVAF without previous ICH	70%	72	USA and Europe	707	[49]
	Death	0.012		Beta	In hospital mortality of Percutaneous Coronary Intervention. Assuming percutaneous procedure in patients with ICH and NVAF is comparable to population who undergo first PCI.	67%	64	USA	120000 to 280000 per trial	[54]
Complication	Death	0.004		Beta	Estimated with an expert based on literature.					[20,49]
Stable	2nd event ICH	0.002		Beta	Patients with NVAF without previous ICH	70%	73	USA and Europe	1114	[50]

	2nd event Ischemic Stroke	0.016		Beta	Patients with NVAF without previous ICH	70%	73	USA and Europe	1114	[50]
	Death	0.030	0.019-0.045	Beta	Patients with NVAF without previous ICH	70%	72	USA and Europe	707	[49]
ICH NVAF Good condition	2nd event ICH (NT)	0.013		Beta	34 events in 2533 patient years. Patients with previous ICH and no treatment.	55%	67	Finland	680	[9]
	2nd event Ischemic Stroke (NT)	0.023	0.154-0.334	Beta	28 events in 1210 patient years	50%	70	Scotland	417	[55]
	Death (NT)	0.191	0.160-0.226	Beta	130 events in 682 patient years	62%	78	Denmark	1752	[56]
	2nd event ICH (VKA)	1.10*	0.96-1.26	Lognormal	Warfarin after ICH, 1 year after PICH, compared to no treatment	60%	73	USA	706	[18]
	2nd event Ischemic Stroke (VKA)	0.46*	0.28-0.75	Lognormal	Warfarin after ICH, 1 year after PICH, compared to no treatment	60%	73	USA	706	[18]
	Death (VKA)	0.32*	0.15-0.66	Lognormal	Warfarin after ICH, 1 year after PICH, compared to no treatment	60%	73	USA	706	[18]

	2nd event ICH (NOAC)	0.42*	ln(RR) -0.87 SE 0.17	Lognormal	Apixaban, no PICH (Apixaban VS Warfarin)	1 male	75	Norway	1 Base Case	[16]
	2nd event Ischemic Stroke (NOAC)	0.92*	ln(RR) -0.08 SE 0.11	Lognormal	Apixaban, no PICH (Apixaban VS Warfarin)	1 male	75	Norway	1 Base Case	[16]
	Death (NOAC)	0.89*	ln(RR) -0.12 SE 0.06	Lognormal	Apixaban, no PICH (Apixaban VS Warfarin)	1 male	75	Norway	1 Base Case	[16]
2nd Event 2nd ICH	Reasonable good condition (mRS 0-3)	0.60	0.00-0.97	Dirichlet	mRS score after recurrent ICH with VKA 12 reasonable good condition /20 recurrent ICH	61%	74	Italie	267	[10]
	Poor condition (mRS 4-5)	0.15	0.00-0.69	Dirichlet	mRS score after recurrent ICH with VKA 3 poor condition /20 recurrent ICH	61%	74	Italie	267	[10]
	Death	0.25	0.01-0.80	Dirichlet	mRS score after recurrent ICH with VKA 5 deaths /20 recurrent ICH	61%	74	Italie	267	[10]
2nd Event Ischemic Stroke	Reasonable good condition (mRS 0-3)	0.67	0.63-0.72	Dirichlet	2196 persons of the 3266 with recurrent ischemic stroke after previous ischemic stroke end up in	64%	66	35 different western countries	40664	[19]

					mRS 0-3 after 3 months after recurrence = 67,24%					
	Poor condition (mRS 4-5)	0.18	0.15-0.22	Dirichlet	598 persons of the 3266 with recurrent ischemic stroke after previous ischemic stroke end up in mRS 4-5 after 3 months after recurrence = 18,31%	64%	66	35 different western countries	40664	[19]
	Death	0.15	0.11-0.18	Dirichlet	472 persons of the 3266 with recurrent ischemic stroke after previous ischemic stroke end up in mRS 6 (death) after 3 months after recurrence = 14,45%	64%	66	35 different western countries	40664	[19]
Poor condition (mRS 4-5)	Death	0.22		Beta	207/771 in 4 years	53%	73	UK	728	[57]
Reasonable good condition (mRS 0-3)	Death	0.08		Beta	96/155 in 4 years	53%	73	UK	728	[57]

Table a3 Utilities

Variable	**Utility**	**Disutility**	**SE**	**Distribution**		**Source**

NVAF ICH Good condition	0.86		0.031	Beta		[58]
LAAO		0.06	0.038	Beta	To retrieve the utility decrement and its low and high range multiple studies are used.	[59,60]
Complications		0.11	0.013	Beta	The utility decrement of different complications is retrieved from Sullivan (2005,2006) and is normalized with the complication rate of Holmes (2009)	[49,52,53]
Stable	0.86		0.031	Beta		[58]
2nd event ICH		0.13850	0.011	Beta	Decrement for ICH	[53]
2nd event Ischemic Stroke		0.13850	0.011	Beta	Decrement for ischemic stroke	[53]
Reasonably Good condition	0.60		0.041	Beta	Moderate Stroke	[51]
Poor condition	0.45		0.074	Beta	Severe Stroke	[51]
Death	0					

Appendix C Costs with population description

Costs table with explanation of which costs are included in the model.

Table a4 Costs

Variable	Costs (€)	Distribution	Original price	Country	Year	Currency	Indirect costs	Source
NVAF ICH Good condition (mRS 0-2)	40,544	Gamma	€39,984.-	Sweden	2016	Euros	Yes	[61]
2nd Event Ischemic Stroke	31,230 (4010 SD)	Gamma	€29,484.2	Netherlands	2012	Euros	Yes	[62]
2nd Event ICH	31,230 (4010 SD)	Gamma	€29,484.2	Netherlands	2012	Euros	Yes	[62]
Reasonably Good condition (mRS 0-3)	60,114	Gamma	€59,284.5	Sweden	2016	Euros	Yes	[61]
Poor condition (mRS 4-5)	179,679	Gamma	€177,198	Sweden	2016	Euros	Yes	[61]
Death (mRS 6)	56,430	Gamma	€55,651	Sweden	2016	Euros	Yes	[61]
Warfarin (VKA)	125	Gamma	€121	Norway	2013	Euros	No	[16]
INR monitoring costs	143 ($\alpha = 3.52$ $\beta = 39.17$)	Gamma	€138	Netherlands	2013	Euros	No	[15]
Apixaban (NOAC)	818	Gamma	€817.6	Netherlands	2018	Euros	No	[63]
LAAO	13,107	Gamma	€13,107	Netherlands	2017	Euros	No	[14]
Complications	14,665	Gamma	$22,092.86*0.537 $9,164.43*0.390	United States	2014	US Dollar	No	[49,64]

			$57,006.20*0.073					
Stable	40,544	Gamma	€39,984.- Assuming the same as NVAF ICH Good condition	Sweden	2016	Euros	yes	[61]

Costs of complications is calculated using two different studies. In Holmes (2009) [49], the incidence rate of het complications in mentioned. In Freeman (2016) the costs of the complications was mentioned. These costs were gamma distributed and normalized, to get one estimate of the complication costs. The low and high bound of the estimate are the lowest and highest price of the combined costs.

Appendix D Incremental costs, incremental QALY of VKA, NOAC and LAAO compared to no treatment.

Table a5 Costs and Qalys, incremental Costs and QALYs Riskgroups

		NT		VKA		NOAC		LAAO	
		Non-Lobar	Lobar	Non-Lobar	Lobar	Non-Lobar	Lobar	Non-Lobar	Lobar
IS Low ICH Low	Costs	281904,68	286272,07	372025,76	373614,60	380667,14	381912,72	376990,16	377370,08
	QALY	4,09	4,07	6,02	5,88	6,26	6,10	7,07	6,90
	Incremental Costs			90121,08	87342,54	98762,46	95640,66	95085,48	91098,01
	Incremental QALY			1,93	1,81	2,17	2,03	2,98	2,83
IS Medium ICH Low	Costs	307199,99	310083,35	388328,40	388777,36	395961,74	396114,86	388120,43	387731,40
	QALY	4,07	4,05	5,56	5,47	5,73	5,63	6,47	6,36
	Incremental Costs			81128,41	78694,01	88761,75	86031,51	80920,44	77648,05
	Incremental QALY			1,50	1,42	1,66	1,58	2,41	2,31
IS Low ICH Medium	Costs	285177,33	289309,92	373306,01	374743,52	381695,56	382803,40	377416,84	377716,38
	QALY	4,07	4,05	5,91	5,79	6,14	5,99	6,94	6,78
	Incremental Costs			88128,68	85433,59	96518,23	93493,48	92239,50	88406,46

	Incremental QALY			1,84	1,73	2,07	1,94	2,87	2,72
IS Medium ICH Medium	**Costs**	309352,64	312100,84	388711,13	389112,20	396124,87	396243,79	387900,21	387507,09
	QALY	4,05	4,04	5,49	5,41	5,65	5,56	6,39	6,29
	Incremental Costs			79358,50	77011,35	86772,23	84142,95	78547,57	75406,25
	Incremental QALY			1,44	1,37	1,60	1,52	2,33	2,25
IS High ICH Medium	**Costs**	338918,26	340305,59	403933,18	403640,40	409751,51	409271,00	397031,44	396290,90
	QALY	4,04	4,03	5,06	5,01	5,16	5,11	5,84	5,78
	Incremental Costs			65014,92	63334,81	70833,25	68965,41	58113,19	55985,31
	Incremental QALY			1,02	0,98	1,12	1,07	1,79	1,75
IS Medium ICH High	**Costs**	311539,34	314138,63	389095,68	389435,49	396292,62	396362,90	387680,23	387268,81
	QALY	4,04	4,03	5,43	5,35	5,58	5,49	6,31	6,21
	Incremental Costs			77556,34	75296,86	84753,29	82224,28	76140,89	73130,18
	Incremental QALY			1,38	1,32	1,53	1,46	2,27	2,18
IS High	**Costs**	340089,61	341412,94	403831,09	403535,58	409507,14	409031,63	396581,96	395860,15

ICH High	**QALY**	4,04	4,03	5,02	4,98	5,12	5,07	5,79	5,74
	Incremental Costs			741,48	62122,64	69417,53	67618,69	56492,34	54447,21
	Incremental QALY			0,99	0,95	1,08	1,04	1,76	1,71