An estimation of the costs of producing an incremental QALY for patients suffering acute ischemic stroke in Denmark

A discussion of opportunity costs

AALBORG UNIVERSITY
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Master's thesis, 10th semester

Group 10025

Medicine with Industrial Specialisation
Medical Market Access

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STUDENT REPORT

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Abstract:

Objective: The aim of this project is to estimate the costs of producing one incremental quality-adjusted life year (QALY) in Denmark for patients suffering acute ischemic stroke (AIS). This will be used to assess opportunity costs in the Danish health care sector.
Methods: A Markov model is used to estimate costs and QALY for two alternatives; one reflecting the current treatment of AIS and one reflecting a hypothetical alternative with no treatment strategy. A limited societal perspective is taken, and input parameters for the model are primarily found through systematic literature searches.
Results: The results show that the costs per incremental QALY is DKK 224,146.62. However, due to assumptions, a large uncertainty on the results is present.
Discussion: Firstly, methods used for estimating costs and QALY are discussed, followed by a comparison to other studies. This is a novel way of using a Markov model to estimate opportunity costs. The method is exact in estimating costs of AIS, but has low generalizability and can not be transferred directly to other areas. Lastly, the importance of prioritization in health care is emphasized.
Conclusion: In Denmark, the costs of producing one incremental QALY for AIS patients are DKK 224,146.62. Further research in different disease areas is needed to estimate opportunity costs in the Danish health care sector.

A Danish abstract can be found in appendix A.

Preface

The master's thesis is written by group 20gr10025, Medicine with Industrial Specialisation, Medical Market Access, at Aalborg University spring 2020. The project is written in collaboration with Amgros I/S, but is intended for health economists in Denmark seeking inspiration for estimating the costs of producing a QALY.

The project consists of the following chapters: Introduction, background, scope, methods, results, discussion, and conclusion. Supplemental data and results can be found in the Appendices. When abbreviations are used, the full word or expression is written immediately followed by the abbreviation, when first mentioned. Hereafter, only the abbreviation is used. Tables and figures are all captioned with a table or figure number as well as text below. If a table or figure does not have a reference, it is composed by the group.

We, as a group, would like to thank our main supervisor at Aalborg University Lars Holger Ehlers for his guidance and professional counseling during the entire process. Furthermore, we would like to thank Sune Lindgaard and Line Brøns Jensen from Amgros I/S for their advice and ability to always change our mood for the better during our endeavors at writing this thesis in the challenging times of the COVID-19 pandemic.

Aalborg University, May 26, 2020

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Chapter 1

Introduction

The Danish Medicines Council (DMC) is responsible for evaluating new medical treatments and decide whether to use these as possible standard treatments. Previously, clinical effect was evaluated using a scale of added clinical benefit (see appendix B), which was used as a basis for price negotiations handled by Amgros I/S.[1] From January 2021, the DMC will begin using quality-adjusted life years (QALY) as the effect measure instead of added clinical benefit[2; 3]. QALY will be implemented to help providing a more transparent decision-making process and making decisions on an informed basis[4]. However, QALY will not stand alone, but criteria such as severity, caution, and rarity will also be considered[3]. QALY is a generic measure, that makes comparison across disease areas possible, and therefore an estimation of opportunity costs is interesting in order to optimize allocation of the available resources to get the highest amount of welfare possible.[5]

1.1 Aim

The aim of this project is: *to estimate the costs of producing one incremental QALY for patients suffering acute ischemic stroke in Denmark.*

The results will be used in a discussion of opportunity costs in the Danish health-care sector.

Two scenarios will be compared in a Markov Model with a limited societal perspective. One scenario reflecting the current treatment strategy, and the other reflecting a no treatment strategy with no health-care sector at all. These are compared using an incremental cost-effectiveness ratio (ICER) because the aim is to estimate the costs of an incremental QALY and not just a QALY.

The result from the ICER-calculation is used in an attempt to estimate opportunity costs in the health-care sector in Denmark. This leads to a discussion of ways to estimate cost-effectiveness thresholds (CET) and opportunity costs in health-care.

1.2 Quality-adjusted life years

QALY is a well-renowned method of estimating the effect of medical interventions, partly because it takes both health-related quality of life (HRQoL) and length of life into consideration, and partly because it is a generic measure[5; 6]. The basic concept of QALY is

that "*a QALY is a QALY is a QALY*" and that all QALYs are valued equally, providing a strong basis for comparisons across disease areas[7]. Some interventions might extend length of life, some might increase HRQoL and some might do both, but since QALY can represent all combinations, it is a commonly-used effect measure for health economic evaluations[5].

1.3 Cost-utility analysis

Cost-utility analysis (CUA) is a sub-type of cost-effectiveness analysis and is the golden standard in health economic evaluations because it uses utility as effect measure. Utility is a measure of health-related quality of life (HRQoL) and can be transformed to QALY by adding a temporal aspect.[5; 8] The benefit of using a CUA is the possibility of estimating opportunity costs by comparing the benefits obtained from implementing a new intervention with the benefits lost from replacing another intervention. The difference between the benefits that could be achieved by implementing an intervention and the benefits foregone by not choosing to implement another intervention is called the opportunity costs. Estimation of opportunity costs could help decision-makers because it becomes apparent how many benefits are foregone by implementing a new and more expensive intervention.[5; 9]

For the DMC to better make decisions about implementing new interventions and for Amgros I/S to establish a stronger foundation for price negotiations, it would be interesting to investigate the costs of producing an incremental QALY in the health-care sector in Denmark. However, for this project a narrower medical specialty, acute ischemic stroke (AIS), is chosen, since an investigation of the entire health-care sector is beyond the scope of this master's thesis. The results could help estimate the opportunity costs when implementing new interventions.

1.3.1 Acute ischemic stroke

AIS is the third-most-expensive disease in Denmark and successful treatment of AIS results in a high QALY gain[10]. Furthermore, AIS is a common disease with an annual incidence of 15,000 resulting in a loss of approximately 8,600 life years annually[11]. AIS will be used in the investigation of the costs of producing an incremental QALY in Denmark.

Chapter 2

Acute Ischemic Stroke

2.1 Pathophysiology and epidemiology of stroke

In Denmark, stroke is the fourth leading cause of death with a yearly incidence of 15,000. Stroke can be divided into two distinct subgroups called acute ischemic stroke (AIS) and hemorrhaging stroke (ICH). Approximately 85% of all strokes are ischemic, with vascular occlusion being the most frequent cause. 15% of strokes are caused by a cerebral hemorrhage often due to an intracerebral bleed.[12; 13] The World Health Organization (WHO) defines stroke as *"rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin"*[13].

90% of all stroke patients are 60 years or older and age is the biggest non-modifiable risk factor of stroke. The biggest modifiable risk factors are hypertension, smoking, diabetes mellitus, hypercholesterolemia, and inactivity.[12; 13]

2.2 Complications and prognosis

The annual survival rate of AIS is 70-75%[12]. The survival rate is lower for ICH with only 46% being alive after one year[14]. Furthermore, the sequelae are more severe for ICH patients than for AIS patients. Generally, the prognosis after stroke is not good and 40-70% patients are deceased within five years. Six months after a stroke approximately one-quarter of patients are rehabilitated without significant loss of function. The rest usually have life-long complications as few patients ameliorate after six months.[12]

Complications include but are not limited to new stroke(s), pneumonia, urinary tract infection, incontinence, deep vein thrombosis, embolus, neurogenic pain, as well as depression, anxiety, and other emotional symptoms.[12]

2.3 Treatment of stroke

DMC and its predecessor council 'Danish Council for the Use of Expensive Hospital Medicine' (Rådet for Anvendelse af Dyr Sygehusmedicin, abbreviated RADS) have not issued any formal treatment guidelines for stroke. However, the Danish Neurological Society develop national treatment guidelines for different neurological disorders including stroke.[15] These guidelines are called nNBV and will be used below to elaborate on the

treatment of stroke. Some of the Danish Regions have made their own guidelines, however, these are often based on nNBV[16].

Medical treatment varies depending on the type of stroke. The aim of treating AIS is to dissolve the clot. Intravenous thrombolysis (tPA) is only administered within the first 4,5 hours after stroke onset[17]. AIS can also be treated surgically with endovascular therapy (thrombectomy, abbreviated EVT) depending on the size of the clot.[18; 19] Surgical treatment is only performed within the first 24 hours [17]. Initially, all patients are treated with anti-thrombotic drugs (AT) including acetylsalicylic acid[12; 20]. After diagnosis, the drug clopidogrel is first-line treatment and used as prophylaxis[20].

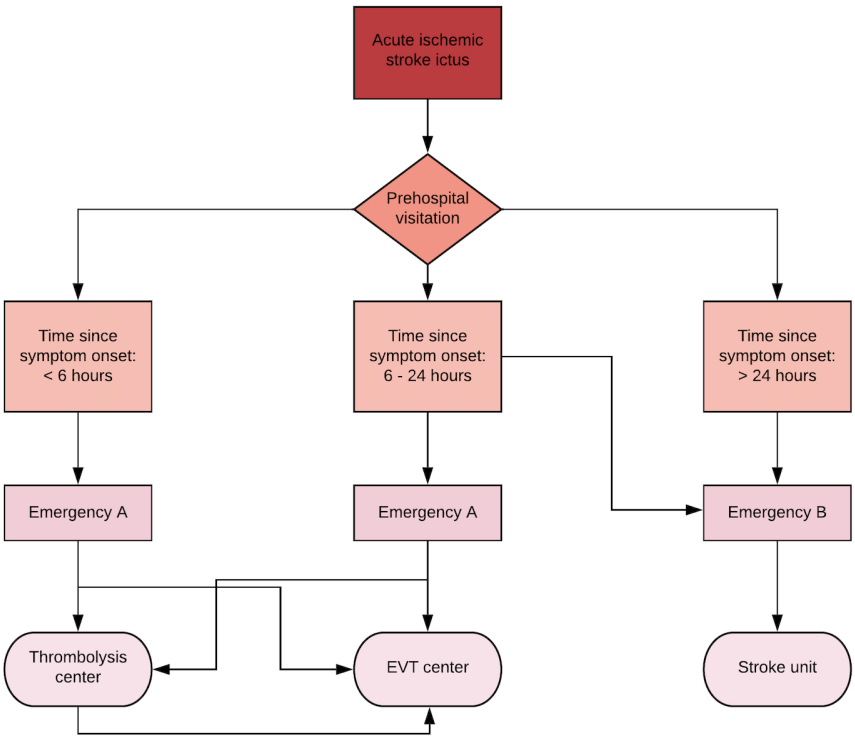

Figure 2.1: Overview of the patient flow following a diagnosis of acute ischemic stroke. Adapted from Danish treatment guidelines [18]. Please note that a thrombolysis center and EVT center is always a part of a stroke unit. In Denmark, eight centers administer tPA and three centers administer EVT and tPA.[21] EVT: Endovascular therapy

The most significant factor in the treatment of AIS is time. The sooner the patient receives treatment, the higher probability of a positive outcome.[22; 18; 19]. Patients are transported by ambulance to either a thrombolysis center, EVT center, or stroke unit depending on their symptoms (see figure 2.1). Transportation by ambulance can be categorized as 'Emergency A', where the ambulance takes on blue lights and goes to the hospital as fast as possible, and 'Emergency B', where the patient is picked up by an ambulance and taken directly to the hospital without blue lights.

2.4 Modified Rankin scale

The modified Rankin scale (mRS) is a tool used to measure levels of functional disability after AIS and other brain injuries[23; 24; 25; 26]. It is a standard tool in clinical trials when evaluating the effect of treatment[24]. mRS is a scale ranging from 0-6, where mRS6 is death. mRS0-2 can be classified as good functional outcomes and mRS3-6 as poor functional outcomes[27; 28]. The seven categories can be seen below in table 2.1.

mRS	Symptoms	Description
0	No symptoms	—
1	No significant disability	Able to carry out all usual activities, despite some symptoms.
2	Slight disability	Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Moderate disability	Requires some help, but able to walk unassisted.
4	Moderate severe disability	Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5	Severe disability	Requires constant nursing care and attention, bedridden, incontinent.
6	Dead	—

Table 2.1: Overview of the modified Rankin scale including symptoms and a description hereof. mRS: Modified Rankin scale. Adapted from Broderick et al.(2017)[26].

Chapter 3

Methods

This chapter will describe the methods used in this project for estimating the costs of producing an incremental QALY when treating AIS in Denmark. Firstly, the decision analytic model is described followed by the procedure for a systematic literature search. Furthermore, a thorough presentation of the structure of the model and the input parameters found in the literature search is given and lastly, different sensitivity analyses are described.

3.1 Decision analytic model

In this project, a Markov model is used to estimate the costs of producing an incremental QALY in Denmark. A Markov model is a type of decision analytic model, which is suitable for chronic diseases or for diseases with long recovery time, such as AIS.[5; 6] The Markov model is a simplification of the real world and will, therefore, include assumptions. Furthermore, using a Markov model enables the possibility of including multiple studies[5], which will also be done in the current project.

The target population is adults with AIS in Denmark. The incidence rate of stroke is highest at the age of 65 and up[11], and therefore 65 years was used as start age in the model. The time horizon is set to 30 years.

Denmark and the Danish health-care system is the setting for the model. Both primary and secondary sector are included as well as costs for pre-hospital and emergency care. In Denmark, the health-care system can be characterized as a Beveridge system, with most costs accruing to the public sector and only few out-of-pocket expenses for patients[8].

A limited societal perspective is chosen to include all relevant, incremental costs and effects. This perspective is recommended by the DMC and Amgros I/S.[29]

3.1.1 Alternatives

In this project, two different approaches to AIS are compared; one alternative called 'current treatment strategy' and one alternative called 'no treatment strategy'. The latter alternative is chosen to reflect a scenario with no health-care system because the aim of the study is to investigate the costs of producing one incremental QALY in Denmark. It is assumed that 100% of patients in the 'current treatment strategy' alternative is treated

and that 0% of patients in the 'no treatment strategy' are treated.

3.2 Literature searches

To collect data for the 'current treatment strategy' branch in the Markov model, multiple systematic literature searches and chain searches were performed to collect the best, available empirical evidence for each parameter. The literature searches were carried out in the medical databases PubMed and Embase and were structured as PICO-searches[30]. Different search terms were used to collect data on utility and transition probabilities. 'Population' is patients with AIS, 'intervention' is the treatment types, and 'outcome' differs between the two searches - either utility for the first search or risk of recurrence, risk of ending in the mRS-states, and mortality for the second search. Examples of controlled terms and free-text words are stroke, brain ischemia, modified Rankin scale, mRS, utility, Quality-adjusted life years, probability, and clopidogrel. For details on the literature searches, see appendix C.

All articles from the literature search were reviewed by both authors and sorted in three stages, firstly by title, then by abstract, and finally by reading full text (See figure 3.1).

3.2.1 Challenges with the 'no treatment strategy' branch

For the 'no treatment strategy' branch no empirical evidence was discovered, most likely because the alternative is purely hypothetical and only applied to the model to estimate incremental costs and effects. Therefore, inputs for the model were not found in the literature search but estimated by consulting a clinical expert (See section 3.9).

3.2.2 Inclusion and exclusion criteria

A filter was added to exclude literature written in other languages than Danish and English. Furthermore, filters such as systematic review, meta-analysis, and randomized controlled trials were added to secure literature from the top of the hierarchy of evidence[31]. Articles based on a patient population not usually comparable to the Danish population were excluded, for example developing countries and countries in Asia. Literature was excluded if mRS5 and mRS6 were grouped as one category and if trials investigated treatments not currently used in Denmark. Studies providing data from Denmark were preferred. The result of the literature search is shown in figure 3.1.

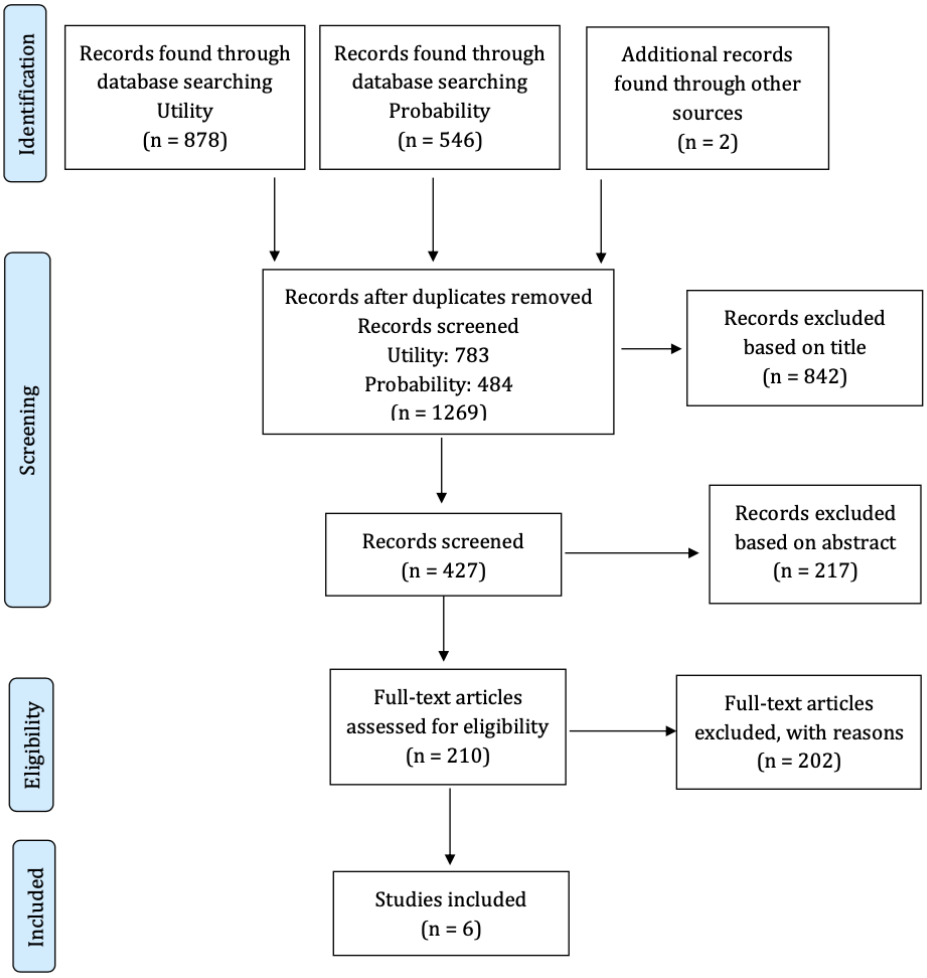

Figure 3.1: Flowchart showing results from the systematic literature searches and chain searches. Adapted from PRISMA[32].

The literature search resulted in a total of ten relevant articles including one meta-analysis, four studies/trials, and one Health Technology Assessment (HTA). After reading full texts, the quality of the articles was assessed. The assessment led to exclusion of multiple articles and in the end, six articles were included.

3.2.3 Assessing quality of evidence

Quality of evidence in the studies was assessed using either the PRISMA checklist or the GRADE approach. PRISMA is used for systematic reviews and meta-analyses while GRADE is used for randomized controlled trials (RCT) and observational studies[32; 33].

3.2.3.1 PRISMA checklist

Quality of the meta-analysis[34] found in the literature search was assessed using the PRISMA checklist, however the article lacked information on 'risk of bias' from the five

included RCTs. Risk of bias for these RCTs was evaluated using the GRADE approach.

Beyond the lack of risk of bias, the PRISMA checklist showed no shortcomings in the meta-analysis, and data was deemed useful in the current project. The PRISMA checklist is shown in appendix D.2.1.

3.2.3.2 The GRADE approach

The GRADE approach makes it possible to up- or downgrade confidence in RCTs and observational studies. It is a classification system with a scale of *high*, *moderate*, *low* and *very low* quality. Observational studies are classified as low quality of evidence and can only be upgraded. RCTs are classified as high quality of evidence, and can only be downgraded.[33]

Ratings of the included studies are seen below in table 3.1.

Author	Risk of bias	Inconsistency	Indirectness	Impresicion	**GRADE**
GRADE of Randomized Controlled Trials					
Berkhemer et al. (2015) †	—	—	—	—	**High**
Jovin et al. (2015) †	—	—	—	—	**High**
Campbell et al. (2015) †	—	—	↓	—	**Moderate**
Saver et al. (2015) †	—	—	—	—	**High**
Goyal et al. (2015) †	—	—	—	—	**High**
Ciccone et al. (2015) [35]	—	↓	↓	—	**Low**
GRADE of Observational studies					
Ali et al. (2016) [36]	↑	—	↑	↑	**Moderate**
Stahmeyer et al. (2019) [37]	↑	—	—	↑	**Moderate**
Slot et al. (2009) [38]	—	—	↑	↑	**Low**

Table 3.1: Rating of included studies using the GRADE approach. A '†' indicates that the study is included in the meta-analysis by Goyal et al.(2016)[34].

The studies by Slot et al.(2009) and Ciccone et al.(2013) were rated as *low* quality of evidence, but were included since no other studies with useful data were found. Further information about the results of GRADE is shown in appendix D.

3.3 Structure of Markov model

The Markov model is built using TreeAge Pro Healthcare 2020 (20.1.2) and will include mRS-states, which is characteristic for AIS. mRS6/death is the only absorbing state in the model.

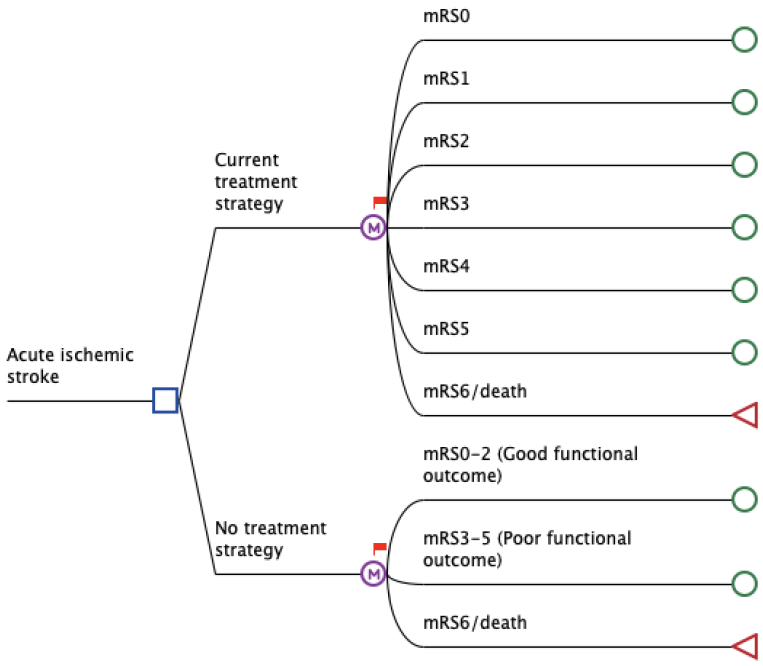

Figure 3.2: Overview of the Markov model. Some branches are collapsed for simplicity.

The decision node (marked with a square in figure 3.2) splits into two branches called 'current treatment strategy' and 'no treatment strategy'. These scenarios reflect the two alternatives being compared in this project. The full tree is included in appendix G.

3.3.1 Half-cycle corrections

Normally, costs and effects accrue to each state at the beginning of a cycle. Half-cycle corrections (HCC) are performed to account for the fact that transitions do not happen step-wise, as modeled in a Markov model, but is a continuous, smooth function, where rewards are counted in the middle of each cycle[39]. HCC is usually performed on utility values and costs, but in this project initial treatment costs are not half-cycle corrected. This would result in unrealistically low costs of treating AIS in the hospital.

3.3.2 Cycle length

AIS is a rapidly progressing disease and therefore the cycle length should be short[5]. The cycle length is three months and is based on available evidence showing that the first follow-up after AIS is measured after three months.

3.3.3 'Current treatment strategy' branch

The 'current treatment strategy' branch splits into seven branches representing the seven mRS-states(See figure 3.2). Each of these branches include the probability of receiving one

of the four different treatment combinations multiplied by the probability of going to each mRS-state. This means that each branch will include all four treatment combinations. The four treatment combinations are based on Danish treatment guidelines[18]:

A : tPA + AT
B : EVT + AT
C : tPA + EVT + AT
D : AT alone

For example, the probability of going from the current treatment node to mRS0 is:

*(Prob of being treated with A * prob of going to mRS0 if receiving A) +*
*(Prob of being treated with B * prob of going to mRS0 if receiving B) +*
*(Prob of being treated with C * prob of going to mRS0 if receiving C) +*
*(Prob of being treated with D * prob of going to mRS0 if receiving D)*

Please note; A, B, C, and D reflect each of the four treatment combinations but are abbreviated in the equation above for simplification. The probability of being treated with each of four treatment types is described as initial probabilities in section 3.7.

From each of the seven mRS-branches, the patients can either get a recurrence of AIS (henceforth simply called "recurrence"), remit, stay in the same mRS-state, progress, or move to mRS6, which is death and the only absorbing state.

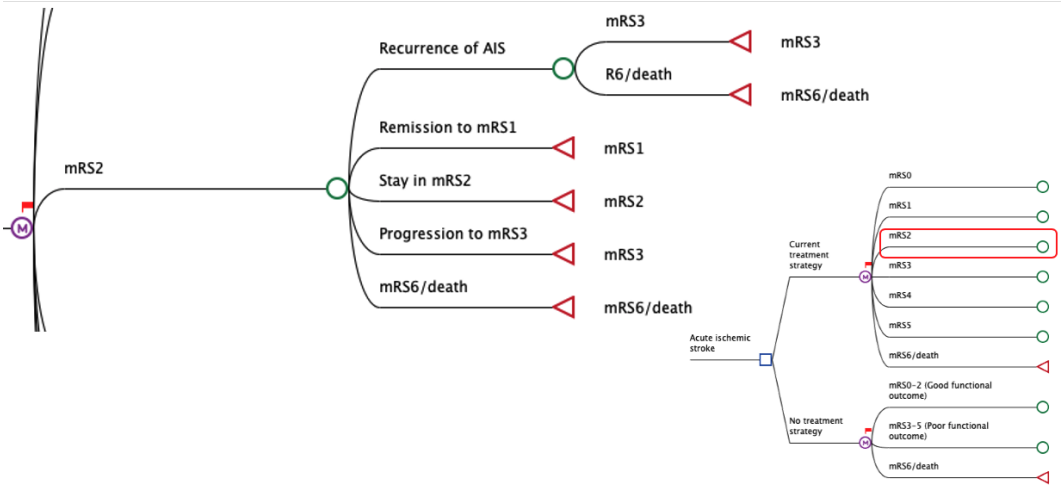

Figure 3.3: A detailed view of the mRS-branches. The figure shows mRS2 as an example - marked with a red square in the small-scale model - however, all mRS-branches are alike.

Patients suffering recurrence is assumed to either progress one mRS-state or die (Assumption validated by clinical expert and M.D. Søren Paaske Johnsen [40]). Patients can only experience one recurrence per cycle. Furthest to the right is the end nodes, also

called jump states in a Markov Model, marked with a triangle. These states represent an mRS-state and each is given a health utility value.

Remission and progression are assumed to only move the patient one mRS-state per cycle. E.g. the patients cannot progress from mRS2 to mRS4 without entering mRS3. This assumption results in the model only allowing patients to move to an mRS-state one state worse or better than the previous cycle.

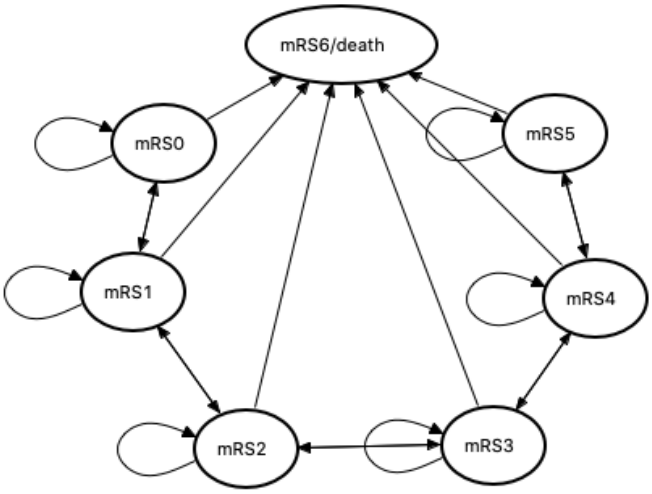

Figure 3.4: State transition diagram for 'current treatment strategy'.

A state transition diagram (see figure 3.4) is another way of depicting a Markov model. It shows all possible transitions between health states in the model.

3.3.4 'No treatment strategy' branch

The 'no treatment strategy' branch splits into three branches representing three health states. The first stage 'good functional outcome' is a grouping of mRS0-2. The second state 'poor functional outcome' is a grouping of mRS3-5 and finally, the third state is mRS6/death (see figure 3.5). From each state it is possible for the patient to either get a recurrence, remit, stay in the same state, progress, or die as in the 'current treatment strategy' branch.

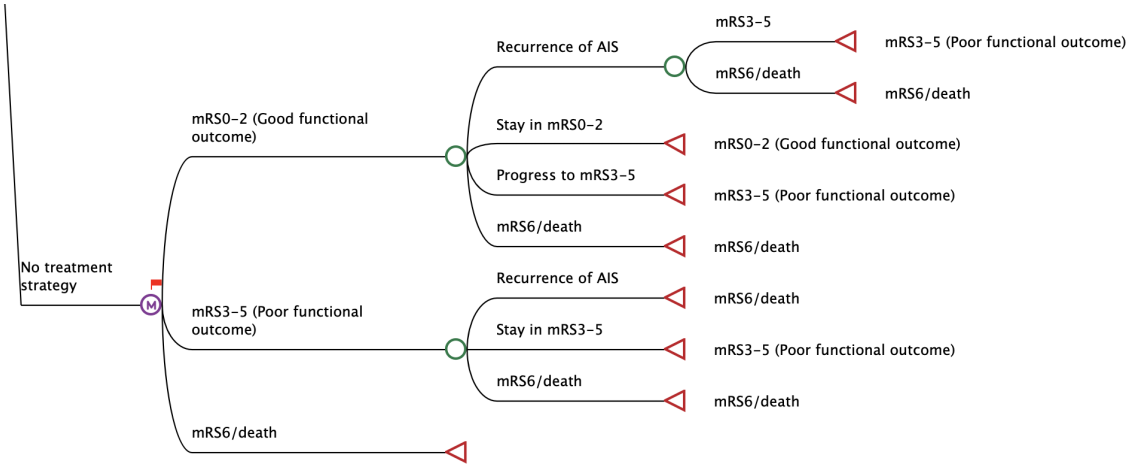

Figure 3.5: A detailed view of the 'no treatment strategy' branch.

As in the 'current treatment strategy' branch, patients can only progress or remit to an mRS-state one state worse than the previous cycle. It is assumed that patients in mRS3-5 can not remit since they do not receive any treatment (see figure 3.6).

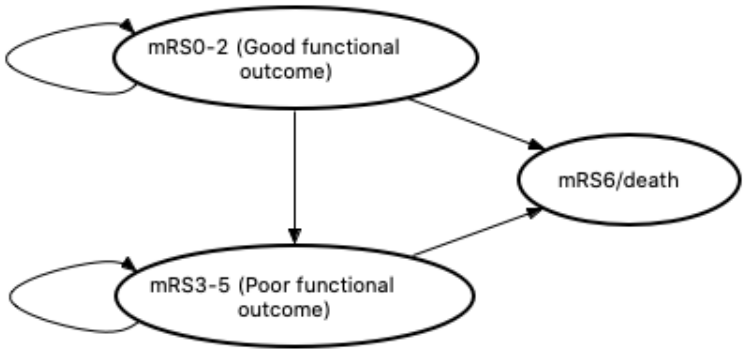

Figure 3.6: State transition diagram for 'no treatment strategy'.

3.4 Discount Rate

Discounting should be applied to all costs and effects incurring after 1 year[29]. Due to limitations in TreeAge Pro software, it was not possible to start discounting in cycle 4, corresponding to one year. Therefore, all cycles from 1 - corresponding to three months - and upwards are discounted, although this is not common practice. Discounting is used to account for a positive rate of time preference, meaning that individuals prefer to receive e.g. increased health utility sooner rather than later [5; 6; 8].

The annual discount rate in Denmark is 4% the first 35 years[41]. Since cycles in this project are three months and not one year, this rate must be converted. Therefore, we wish to calculate the discount rate for three months. This is shown below:

$$1 + annual\ discount\ rate = (1 + r)^n \text{ [42]} \tag{3.1}$$

Where n is the number of cycles per year and r is the discount rate per cycle.

$$\begin{aligned} 1 + 0.04 &= (1 + r)^4 \\ \sqrt[4]{1.04} &= (1 + r) \\ 1 + r &= 1.009853 \\ r &= 1.009853 - 1 \\ r &= 0.009853 = 0.985\% \end{aligned}$$

The discount rate is 0.009853 per cycle.

All costs and effects are discounted using the following equation:

$$present\ value = \frac{future\ value}{(1 + 0.009853)^n} \tag{3.2}$$

Where n is number of cycles.

3.5 Choice of Health Outcome

QALY is chosen as the health outcome because the aim of this project is to investigate the cost of producing one QALY in the Danish health-care system. Furthermore, QALY is the preferred outcome in health economic evaluations and is used in CUA[5].

3.6 Measurement of effectiveness

The effect is measured in health utility and is a single study-based estimate from an observational study by Ali et al.(2016) using EQ-5D-3L utility weights from Denmark[36]. Health utility values for each mRS-state applied to the model can be seen below in table 3.2.

mRS	Health utility value	SD
0	0.91	0.15
1	0.83	0.16
2	0.73	0.16
3	0.61	0.19
4	0.37	0.19
5	-0.02	0.27
6	0	0

Table 3.2: Utility values and related SD for each mRS-state applied to the 'current treatment strategy' branch. mRS: Modified Rankin scale, SD: Standard deviation.

Although negative utility values are rare, this is the case for mRS5. Health utility values showed above in figure 3.2 are added to each mRS-state in the Markov model.

Utility values in the 'no treatment strategy' branch are assumed to correspond to the lowest value in each group from table 3.2 to reflect a worse outcome if patients are not treated at all. The values added to the model are shown in table 3.3.

mRS	Health utility value	SD
0-2	0.73	0.16
3-5	-0.02	0.27
6	0	0

Table 3.3: Utility values and related SD for each mRS-state applied to the 'no treatment strategy' branch. mRS: Modified Rankin scale, SD: Standard deviation.

3.7 Estimating initial probabilities for 'current treatment strategy' branch

Initial probabilities in the Markov model is the division of patients to the seven mRS-states depending on the received treatment. The method for calculating this is described in section 3.3.3. The methods for estimating probabilities is described in the following section.

3.7.1 Probability of receiving treatment

The distribution of patients receiving each of the four treatment combinations is found in Dansk Apopleksiregister[17] and is shown below in table 3.4.

Treatment combination	Distribution (%)
tPA + AT	16
EVT + AT	3
tPA + EVT + AT	3
AT alone	78

Table 3.4: Distribution of patients receiving different treatment combinations[17]. tPA: Thrombolysis, AT: Antithrombotics, EVT: Endovascular therapy.

These probabilities are then multiplied with the probability of ending in each mRS-state after receiving treatment, which will be described in the following.

3.7.2 Probability of health states

Results extracted from Goyal et al.(2016) are shown in 3.5. Probability of the mRS-states is measured at three months, but in this project it is assumed to be constant and therefore added to each cycle. This assumption is validated by the clinical expert[40] and supported by Danish treatment guidelines[17].

mRS (3 months)	tPA + AT (n = 565)	EVT + AT (n = 108)	tPA + EVT + AT (n = 525)	AT alone (n = 80)
0	0.051	0.102	0.099	0.036
1	0.081	0.157	0.177	0.062
2	0.138	0.176	0.194	0.125
3	0.175	0.185	0.166	0.087
4	0.237	0.074	0.173	0.312
5	0.133	0.074	0.059	0.15
6	0.184	0.231	0.137	0.225
Sum of mRS	0.999	0.999	1.005	0.997

Table 3.5: Probabilities of ending up in each mRS-state after 3 months. All results are from Goyal et al.(2016)[34]. The sums do not add up to 1.00 due to rounding. mRS: Modified Rankin scale, tPA: thrombolysis, EVT: thrombectomy, AT: Antithrombotics.

The normalization feature in TreeAge is used to compensate for the fact, that the probabilities do not add up to 1.00.

3.8 Estimating transition probabilities for 'current treatment strategy' branch

In this section, transition probabilities for moving between different mRS-states in the 'current treatment strategy' branch are presented.

3.8.1 Probability values for recurrence

Probabilities for recurrence are extracted from four different studies. Probabilities are shown in table 3.6. Since data is not available for every 3-month cycle in the model, the probabilities will be added to the cycles corresponding to the year.

Risk of recurrence	Applied to cycle	tPA + AT	EVT + AT	tPA+ EVT + AT	AT alone
3 months	0-3	0.022 [35]	0.012 [43]	0.022 [35]	0.033 [44]
1 year	4-7	0.074 [37]			
2 years	8-11	0.037 [37]			
3 years	12-15	0.028 [37]			
4 years	16-19	0.029 [37]			
5 years	20-120	0.026 [37]			

Table 3.6: Risk of getting recurrent ischemic stroke after 3 months and 1-5 years. Sources are shown in [ ]. tPA: Thrombolysis, AT: Antithrombotics, EVT: Thrombectomy.

One RCT provided probabilities for recurrence after three months for patients treated with tPA + AT and tPA + EVT + AT. 70% of these patients received tPA, but no subgroup analyses differentiate between patients receiving tPA and those not receiving tPA.[35] An assumption was made, that all patients in this study received tPA.

Furthermore, the study used for probabilities for 1-5 years does not differentiate between treatment types, and therefore these probabilities will be added to all treatment types[37]. Furthermore it is assumed that the risk of suffering a recurrence is not dependent on mRS-state (Assumption validated by the clinical expert[40]).

3.8.1.1 Mortality after recurrence

Mortality after recurrence is assumed to be the same as mortality for initial AIS because detailed data was not found in the literature. The surviving patients will all increase their mRS-state one level after recurrence. This is marked with a '#' in the Markov model. If a probability is marked with a "#" TreeAge Pro will automatically estimate this probability, so that the final sum equals 1.

3.8.2 Probability of remitting, staying and progressing after stroke

According to the clinical expert, patients will neither progress nor remit after cycle 0[40]. However, the branches representing these two outcomes are included in the model to make sensitivity analyses possible. Uncertainties on these parameters are investigated in section 3.12.

The probability of staying in the same mRS-state is marked with a "#".

3.8.3 Probability values for mortality

One of the observational studies investigates the relative risk of dying in each mRS-state. These relative risks are multiplied with the mortality rate in Denmark to get the prob-

ability of dying in each mRS-state. The authors of the study assume that mRS0-1 has the same risk of dying as the general population, and this assumption is also made in the current project.[38]

The Danish mortality rates were found in the deaths registry made by Statistics Denmark and include different mortality rates for different ages[45]. The data set can be found in appendix E.

mRS	RR
0	1
1	1
2	1.12
3	1.66
4	1.92
5	2.57

Table 3.7: Relative risk of dying in each mRS-state[38]. mRS: Modified Rankin scale, RR: Relative risk.

3.9 Estimating probabilities in 'no treatment strategy' branch

This branch is purely hypothetical since a scenario where AIS is not being treated would be highly unlikely.

3.9.1 Estimating initial probabilities

Initial probabilities for the 'no treatment strategy' branch is estimated via clinical expert Søren Paaske Johnsen[40], since neither literature nor data exist on this topic. The estimations are shown in table 3.8.

mRS	Probability
0-2	0.4
3-5	0.3
6	0.3

Table 3.8: Estimated probabilities of ending in different mRS-states in the 'no treatment strategy' branch[40]. mRS: Modified Rankin scale

3.9.2 Probabilities for recurrent stroke

According to the clinical expert the risk of recurrence is approximately 25% higher than the 'current treatment strategy' branch[40]. Therefore, the risk of recurrence from the 'current treatment strategy' branch is multiplied with 1.25 to provide risk of recurrence in the 'no treatment strategy' branch.

3.9.3 Probability of staying and progressing after stroke

It is assumed, that patients will not progress (Assumption validated by the clinical expert[40]). The probability of progression is set to 0. The probability of staying is marked with a '#'.

3.9.4 Mortality rates

The mortality rate after AIS is estimated by taking the highest relative risk for each group from the article also used in the 'current treatment strategy' branch[38] (see figure 3.9). This method is chosen because no exact data exist. The relative risk is multiplied with the Danish mortality rates (See section 3.8.3).

mRS	RR
0-2	1.12
3-5	2.57

Table 3.9: Relative risk of dying in each mRS-state[38]. mRS: Modified Rankin scale, RR: Relative risk.

The mortality rate after recurrence is assumed to be the same as mRS0-2 since recurrence can only happen to patients in this mRS-state.

3.10 Estimating resources and costs

The following section is used to present monetary costs related to treatment and care of AIS. The costs are estimated in DKK in January 2020-values, and costs from previous years were extrapolated. The consumer price index was used for extrapolation using the formula:

$$Present\ value = \frac{Past\ value * Present\ index\ value}{Past\ index\ value} \tag{3.3}$$

The index value for January 2020 is 103.3[46].

3.10.1 Costs applied to 'current treatment strategy' branch

3.10.1.1 Costs of hospitalization

Diagnostic-related groups (DRG) rates are used to estimate the costs of treating AIS in hospitals. DRG rates are averages calculated annually by the Danish Ministry of Health and include all costs of treating a patient[47].

Description	DRG code	Cost (DKK)	Applied to:	
			Cycle	Patients
Diagnosis of cerebral thrombosis	01SP01	4,996.00	0	All
Treatment with thrombolysis in AIS	01MP11	61,223.00	0	Patients treated with tPA + AT
Intracranial, intraarterial thrombectomy	26MP16	262,444.00	0	Patients treated with EVT + AT and tPA + EVT + AT
Out-patient follow up	23MP04	1,512.00	1	Patients treated with tPA + AT, EVT + AT and tPA + EVT + AT. Only mRS0 to mRS3
Carotid surgery	01MP03	68,444.00	0	84% of all patients
Emergency A	[48; 49]	1,050.00	0	Patients treated with tPA + AT, EVT + AT and tPA + EVT + AT.
Emergency B	[48; 49]	1,125.00	0	Patients treated with AT alone.

Table 3.10: List of DRG rates related to treatment and hospitalization of AIS in 'current treatment strategy' branch. All costs are direct costs. DRG: Diagnosis related group, mRS: Modified Rankin scale.

Costs of treatment and admission in the hospital are listed in table 3.10. The cost of diagnosing AIS is added to all treatment combinations in the model. Costs of treating a patient with tPA + EVT is the same as treating EVT alone. An outpatient follow-up visit is added to patients treated with EVT or tPA in cycle 1[40]. Furthermore, 84% of patients receive carotid surgery, which is also added to the model[17].

Costs of prehospital treatment including patients being transported to the hospital by ambulance are shown in figure 3.10. The costs are based on data from Region Sjælland and Region Nordjylland [48; 49].

3.10.1.2 Costs of rehabilitation and nursing home

Costs of rehabilitation are partially based on DRG rates and partially on results from a Danish HTA on rehabilitation after brain damage[50]. When patients are discharged they receive neurorehabilitation in different facilities depending on their given mRS-state (see table 3.11).

Description	Source (reimbursement code)	Cost (DKK)	Applied to	
			Cycle	Patients
Intensive neurorehabilitation in decentralized unit	[51] (26MP03)	288,330	0	mRS4
Intensive neurorehabilitation in highly specialized unit	[51] (26MP01)	799,223	0	mRS5
Institution rehabilitation	[50]	54,729	1	mRS4 and mRS5
Home care	[50; 52]	14,300	0-75	mRS2
		35,750	0-75	mRS3
		71,500	1-75	mRS4
Physiotherapist, individual	[50; 52]	3,144	1	mRS4 and mRS5
Ergotherapist, individual	[50; 52]	4,788	1	mRS4 and mRS5
Physiotherapist, group	[50; 52]	1,257.60	1	mRS4 and mRS5
Ergotherapist, group	[50; 52]	1,064	1	mRS4 and mRS5

Table 3.11: Rehabilitation costs. All costs are calculated for three months. mRS: Modified Rankin scale.

Costs of rehabilitation are all one-time costs. Costs related to home care are only added to cycle 0-75, because it is assumed that all patients live at a nursing home after the age of 84, corresponding to cycle 76[53].

3.10.1.3 Other costs

Other costs applied to the model include transportation costs for the patients and out-of-pocket payments for clopidogrel. These are shown below in table 3.12.

Description	Source (reimbursement code)	Cost (DKK)	Applied to	
			Cycle	Patients
Clopidogrel, 75 mg/day	Medicinpriser.dk	123.75	0-120	mRS0 to mRS5
GP consultation	[54] (0101)	145.46	0-120	mRS0 to mRS3
			1-120	mRS4 and mRS5
Venous blood sample	[54] (2101)	49.84	0-120	mRS0 to mRS3
			1-120	mRS4 and mRS5
Transportation, patients	[52]	100.00	1	mRS4 and mRS5 †

Table 3.12: Other costs added to the Markov model. †: Transportation costs are added to each trip to rehabilitation with physio- and ergotherapist. GP: General practitioner. mRS: Modified Rankin scale.

The price of clopidogrel is found on medicinpriser.dk on the 30th of April 2020 and was DKK 41.25. One package lasts one month, and therefore the price is multiplied by three to reflect cost per cycle. All patients treated with clopidogrel visit their general practitioner

(GP) once every three months[40]. The costs for this are found in the "Honorartabel" for GPs in Denmark, and reimbursement codes 0101 and 2101 are used[54]. Transportation costs for the patients are defined by DMC to DKK 100 per hospital visit[52].

3.10.1.4 Costs of recurrence

Patients suffering a recurrence is given an extra cost equal to the cost of treating initial AIS in the hospital and the cost of emergency transportation.

3.10.2 Costs applied to 'no treatment strategy' branch

Patients in this treatment strategy do not receive any treatment in the hospital nor any rehabilitation. The only costs added are home care for one-third of patients in mRS0-2 (good functional outcome) and two-thirds of patients in mRS3-5 (poor functional outcome).

3.11 Assumptions

When building a Markov model, assumptions are inevitable [5; 6]. In this project, all assumptions are mentioned throughout this chapter. A full list of assumptions and reasons can be found in appendix F.

3.12 Sensitivity analysis

When making assumptions and estimates in economic evaluations, uncertainties will always occur. In this project, deterministic and probabilistic sensitivity analyses are performed to examine uncertainties. Examples of uncertainties are parameter, methodological, structural, and generalizability uncertainties. A probabilistic sensitivity analysis (PSA) can investigate parameter uncertainty, whereas deterministic analyses can investigate all types of uncertainties. It is good practice to include both types of sensitivity analysis, to examine the reliability of the results. [5; 6; 8]

3.12.1 Deterministic sensitivity analysis

Deterministic sensitivity analyses will be used to examine the effect of each parameter in the model and how a change in perspective would affect the results.

3.12.1.1 Tornado analysis

In this project, a tornado diagram is created to show the impact on the result of a change in each parameter[5; 6]. The results will be depicted in a bar chart, where a wide bar means a high impact on the final result, and in a table showing potential ICER values. The

tornado analysis is performed on all parameters and adjusted with ± 20%. Probabilities of remission and progression are manually changed to 0 - 0.01, as ± 20% of 0 is not possible.

3.12.1.2 Scenario analysis

To reflect the preferred perspective by DMC and Amgros I/S, a limited societal perspective is investigated in the primary analysis. A scenario including nursing homes is investigated in a deterministic analysis. Nursing home costs are found in a Danish HTA[50] and extrapolated from 2008-values to 2020-values. It is assumed that all citizens live at a nursing home after the age of 84, corresponding to cycle 76, and the costs of nursing homes are added to the model from cycle 1-75[53]. All patients in mRS5 will get this added cost.

3.12.1.3 Health-care payer perspective

A change of perspective is investigated with a health-care payer perspective. Costs related to transportation for patients, home care, and clopidogrel are excluded.

The health-care payer perspective includes costs related to GP, treatment in the hospital, neurorehabilitation at a decentralized or highly specialized unit, and all physio- and ergotherapy as well as emergency transportation are included.

3.12.2 Probabilistic sensitivity analysis

A PSA will be used for investigating parameter uncertainties in the Markov model by random sampling of distributions for each parameter, using Monte Carlo simulations. A cost-effectiveness scatter plot will show uncertainty on each treatment strategy alone. The PSA will also provide an incremental cost-effectiveness (ICE) scatter plot showing the distribution of each of the 10,000 iterations looking like a 'cloud'. If the iterations are closely assembled, uncertainty is small.[5]

3.12.2.1 Distributions

Each parameter in the Markov model is assigned a distribution. Costs are gamma-distributed and probabilities are beta-distributed. Normally, utility values are beta distributed, which is restricted by $0 \leq x \leq 1$.[5] However, the utility value for mRS5 is negative, and therefore a normal distribution will be used for all utility values. If a standard deviation (SD) was not available, 20% of the mean was used as SD to reflect uncertainty. This SD was added to all costs and probabilities. The only exceptions of this are the parameters 'probability of remission' and 'probability of progression', where a

triangular distribution was used with 0 as the minimum and 0.01 as maximum. This was done because ± 20% of 0 is not possible.

Chapter 4

Results

Results from the Markov model and different sensitivity analyses will be presented in the following chapter. Analysis and interpretation of results can be found in chapter 5.

4.1 Expected values from the Markov model

The structure of the Markov model is complex, and a simplified, collapsed version is below in figure 4.1 that shows expected values (EV) of the two treatment strategies. The entire model is included in appendix G. Furthest to the left, a decision node branches out into the two different treatment scenarios being compared. From these, a Markov node splits into different health states. Each path leads to a terminal node, from which patients can jump to other health states.

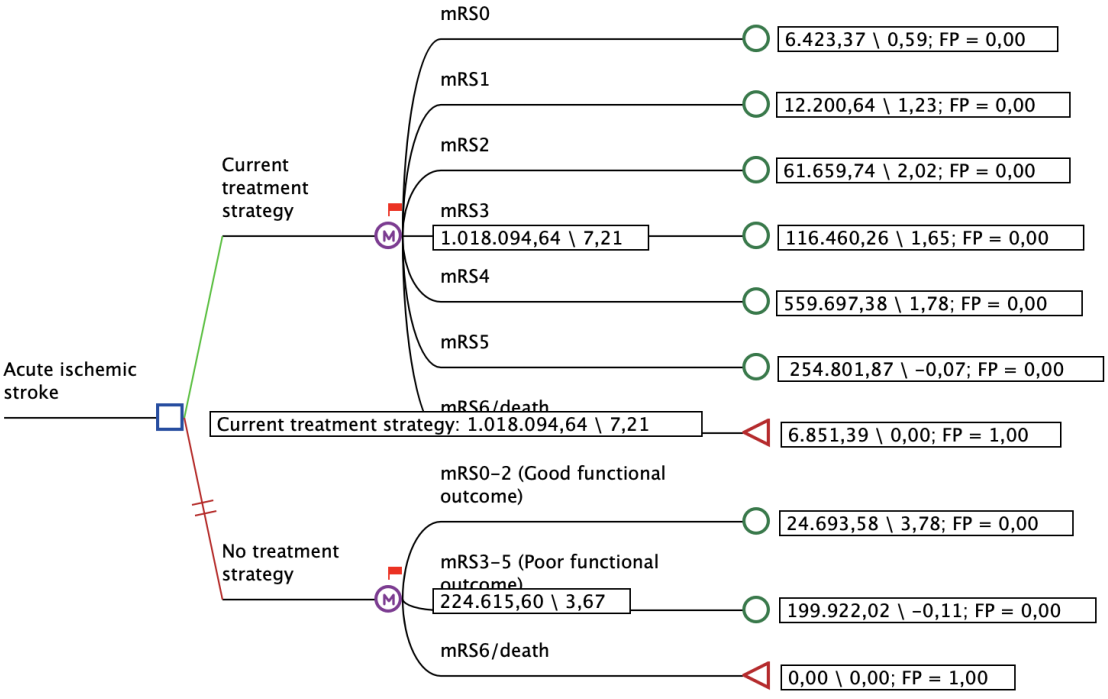

Figure 4.1: A simplified version of the Markov model with expected values.

The boxes to the right show 'FP' which is the final probability of ending in that health state. Since mRS6/death is the only absorbing state, all patients end here.

The 'current treatment strategy' branch shows an EV of DKK 1,018,094.64 and 7,21

QALY. EV of 'no treatment strategy' branch is DKK 224,615.60 and 3,67 QALY. This is also shown below in table 4.1

Treatment strategy	Cost (DKK)	Effect (QALY)
Current treatment	1,018,094.64	7.21
No treatment	224,615.60	3.67

Table 4.1: Expected values from the Markov model. QALY: Quality-adjusted life years.

4.1.1 Incremental cost-effectiveness ratio

Incremental cost-effectiveness ratio (ICER) is calculated using EV from table 4.1 above.

$$ICER = \frac{DKK\ 1{,}018{,}094.64 - DKK\ 224{,}615.60}{7.21\ QALY - 3.67\ QALY}$$

$$ICER = \frac{DKK\ 793{,}479.04}{3.54\ QALY}$$

$$ICER = DKK\ 224,146.62\ per\ QALY$$

The ICER shows that the costs of producing an incremental QALY in the field of AIS is DKK 224,146.62.

4.2 Sensitivity analyses

The following section will include both deterministic and probabilistic sensitivity analyses. The deterministic sensitivity analyses will include one-way, tornado analysis and changes of perspective.

4.2.1 Deterministic sensitivity analyses

4.2.1.1 Tornado analysis

The parameter with the largest impact on the final result is utility value at mRS0-2 followed by multiple utility values. The top 10 most influential parameters are shown below in figure 4.2. The full tornado analysis is shown in appendix I.

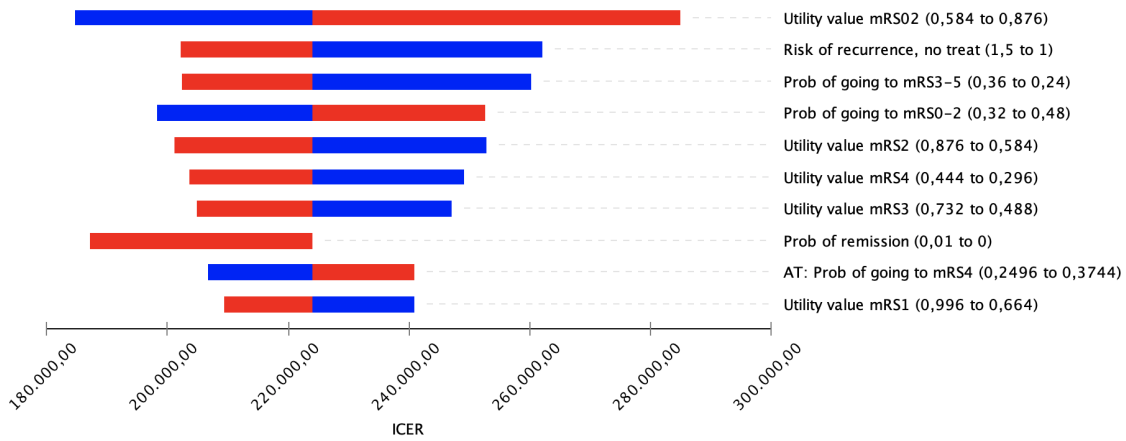

Figure 4.2: A tornado diagram showing the 10 factors with the highest impact on the final result. ICER: Incremental cost-effectiveness ratio.

The widest band at the top belongs to the parameter providing utility values of mRS0-2 in the 'no treatment strategy' branch. A ± 20% change in this parameter would potentially change the ICER to DKK 184,630.28 and DKK 284,915.04 per QALY, respectively. The parameter providing probability of remission is ranging from 0 to 1% and a change in this parameter will result in a lower ICER at DKK 187,058.47 per QALY (See figure 4.2 and table 4.2).

Parameter	Mean (range: ± 20%)	Potential ICER	
		Lower bound	Upper bound
Utility value at mRS02	0.73	184,630.28	284,915.04
Risk of recurrence, no treat	1.25	202,200.03	262,116.75
Prob of going to mRS3-5	0.3	202,333.43	260,107.89
Prob of going to mRS0-2	0.4	198,185.58	252,537.35
Utility value mRS2	0.73	201,131.29	252,897.50
Utility value mRS4	0.37	203,557.62	249,163.18
Utility value mRS3	0.61	204,931.17	247,135.65
Prob of remission	0 †	187,058.47	—
AT: prob of going to mRS4	0.312	206,792.23	240,919.41
Utility value mRS1	0.83	209,458.10	240,856.84

Table 4.2: Overview of the top 10 parameters influencing ICER and how much they would potentially change the result. The '†' indicates that it was not possible to change this parameter with ± 20%, since the mean is 0. Therefore, the range of this parameter is manually adjusted to 0 to 0.01. ICER: Incremental cost-effectiveness ratio.

Table 4.2 shows how much a change in each parameter affects the ICER result.

4.2.1.2 Scenario analysis

A scenario analysis with costs of nursing home is investigated. The results are shown in table 4.3.

Treatment strategy	Cost (DKK)	Effect (QALY)
Current treatment	1,507,283.96	7.21
No treatment	523,823.80	3.67

Table 4.3: Expected values from a deterministic sensitivity analysis changing the perspective from limited societal to also include costs of nursing homes. QALY: Quality-adjusted life years.

EV from the scenario analysis shows that cost of 'current treatment strategy' is DKK 1,507,283.96 and for 'no treatment strategy' is DKK 523,823.80. The ICER is calculated using EV from table 4.3.

$$ICER = \frac{DKK\ 1{,}507{,}283.96 - DKK\ 523{,}823.80}{7.21\ QALY - 3.67\ QALY}$$

$$ICER = DKK\ 281,793.74\ per\ QALY$$

Results of the ICER show that, with the added costs of nursing home, the costs are DKK 281,793.72 per incremental QALY.

4.2.1.3 Health-care payer perspective

A deterministic sensitivity analysis was made with a change to a health-care payer perspective. Results are shown in table 4.4.

Treatment strategy	Cost (DKK)	Effect (QALY)
Current treatment	543,927.20	7.21
No treatment	0	3.67

Table 4.4: Expected values from a deterministic sensitivity analysis changing the perspective from limited societal to health-care payer. QALY: Quality-adjusted life years.

$$ICER = \frac{DKK\ 543{,}927.20 - DKK\ 0}{7.21\ QALY - 3.67\ QALY}$$

$$ICER = DKK\ 155,853.07\ per\ QALY$$

With a change of perspective the ICER shows that the price of producing one QALY is DKK 155,195.27 per incremental QALY.

4.2.2 Probabilistic sensitivity analysis

A PSA with 10,000 iterations was made. Firstly, a CE scatter plot shows uncertainty surrounding the two different treatment strategies. The CE scatter plot below in figure

4.3 shows that uncertainty in 'no treatment strategy' is largest on the utility parameters. Whereas uncertainties on both costs and effects are present in the 'current treatment strategy'.

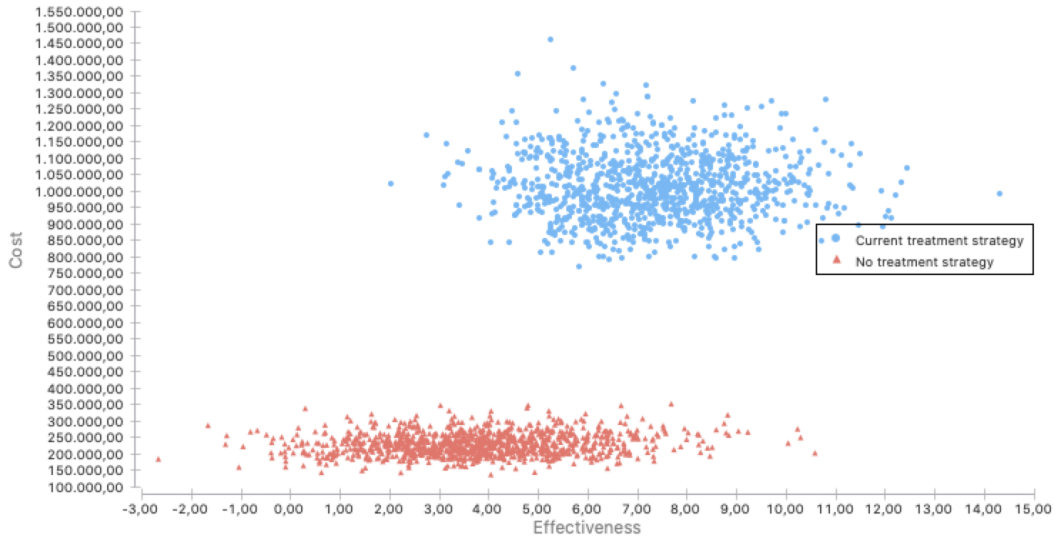

Figure 4.3: Cost-effectiveness scatter plot showing uncertainty surrounding each treatment strategy.

4.2.2.1 Incremental cost-effectiveness scatter plot

The PSA provided an ICE scatter plot showing uncertainty surrounding the ICER. The ellipsis indicates 95% of all iterations. 7.2% of all iterations are placed in the north-west quadrant, indicating that the 'current treatment strategy' produces a negative incremental effect.

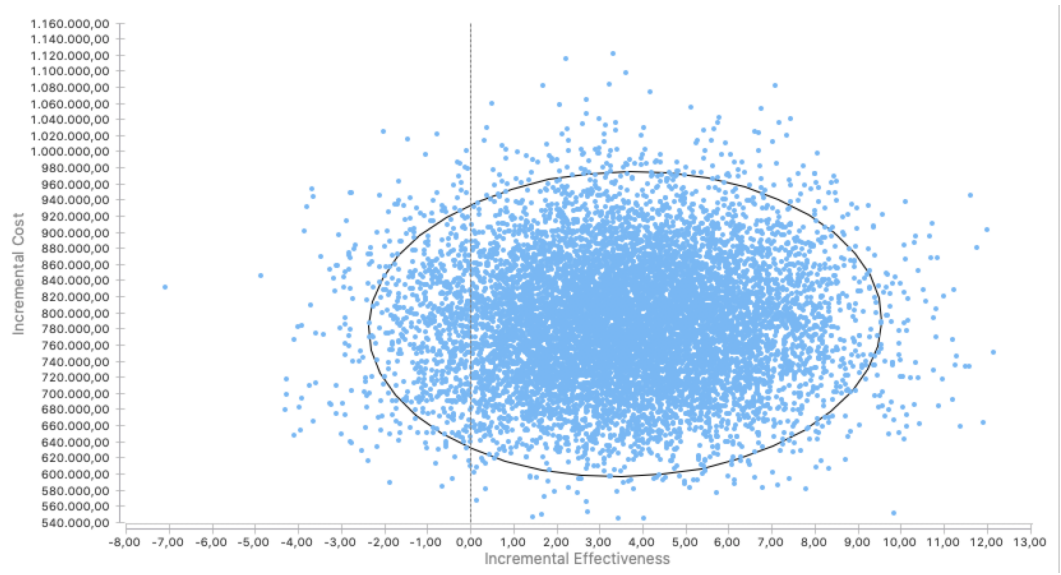

Figure 4.4: Incremental cost-effectiveness scatter plot showing parameter uncertainty. The circle represents 95% of all iterations.

4.2.2.2 Cost-effectiveness acceptability curve

The cost-effectiveness acceptability curve (CEAC) from the PSA shows that the 'current treatment strategy' will never be cost-effective.

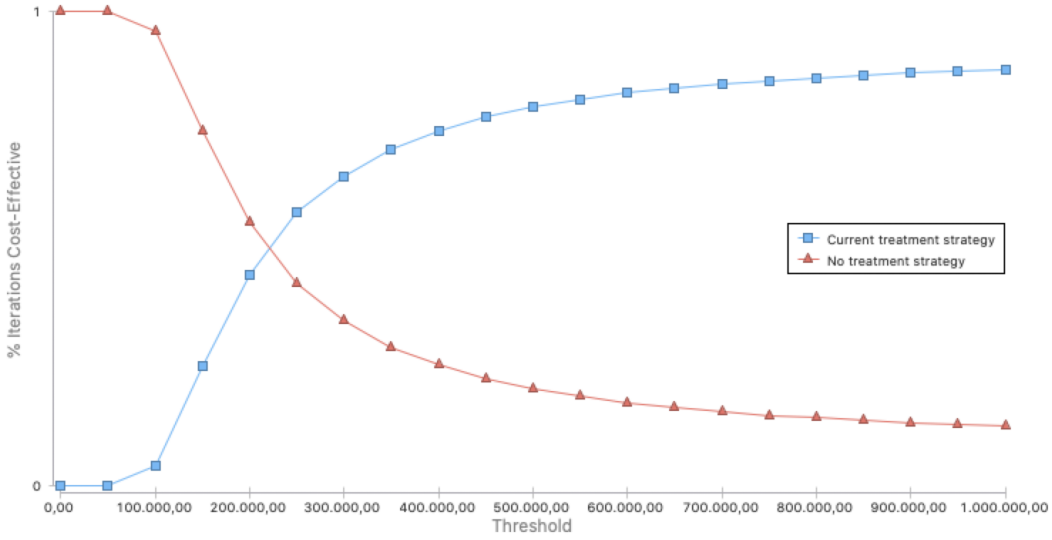

Figure 4.5: Cost-effectiveness acceptability curve showing the probability of each treatment strategy being cost-effective.

Because 7.2% of all iterations in the ICE scatter plot show negative incremental effect the probability of the 'current treatment strategy' being cost-effective will never be 100%. The curve will flatten at 92.8%.

Chapter 5

Analysis and interpretation

The high incremental cost of DKK 793,479.04 between the two treatment strategies can be attributed to the low costs of 'no treatment strategy'. This strategy is inexpensive because the patients are not treated at all, but only receive home care. This strategy is highly unlikely, but is included to show the costs of producing an incremental QALY.

The two treatment strategies do not accumulate many QALYs considering the time horizon is 30 years. This is a result of high mortality rates following stroke and that $\approx$ 100% are dead in cycle 80 for 'current treatment strategy' and in cycle 72 for 'no treatment strategy'. Furthermore, the mRS-states with high utility values are mRS0, mRS1, and mRS2 and the probability of patients being in these states after 50 cycles approximates 0 in both treatment strategies (see appendix H, figure H.1).

The probabilities of remission and progression are 0 and therefore the patients can only stay in the same mRS-state, suffer recurrence - or die. This parameter 'probability of remission' is one of the most influential factors according to the tornado analysis. If patients could remit, costs would decrease and QALY would consequently increase resulting in an ICER of approximately DKK 187.000 per QALY (See table 4.2).

Furthermore, several health utility scores are shown to have a large impact on ICER according to the tornado analysis (see figure 4.2). This is most likely because these values are applied to all cycles and are constant throughout the model. The tornado analysis shows that a change in the probability of ending in different mRS-states when being treated with AT alone can have a large influence on ICER. 78% of all patients will receive this treatment, which is most likely the reason for the large impact on ICER.

5.1 Deterministic sensitivity analyses

The scenario analysis and the change in perspective both show a change in ICER. An addition of nursing home costs would increase the ICER, but the health-care payer perspective would decrease the ICER. The decrease is mainly caused by the removal of continuous costs such as home care, which in this analysis is extracted from each cycle. One-time costs such as GP visits and ambulance costs would not have a large impact on the result. Furthermore, costs of the 'no treatment strategy' are 0 because patients would not receive any treatment or continuous care.

5.2 Probabilistic sensitivity analysis

The CE scatter plot in figure 4.3 shows a horizontal spreading of iterations in the 'no treatment strategy' meaning that uncertainty on utility values are influential. This is presumably due to the high SD of utility values, especially mRS3-5 (Poor functional outcome). The ICE scatter plot shows iterations with a negative incremental effect. This could indicate that there is a risk of the 'current treatment strategy' resulting in a worse clinical outcome than not treating the disease at all. This could result from the fact that patients in mRS5 live longer with the 'current treatment strategy', as this health state has a negative utility value. 7.2% of all iterations are placed in the north-west quadrant. This is also depicted in the CEAC (see figure 4.5), showing that the probability of the 'current treatment strategy' being cost-effective will never reach 100%.

Chapter 6

Discussion

The following chapter is structured as recommended by BMJ[55]. Firstly, the principal findings will be presented followed by a discussion of strengths and weaknesses. Lastly, the meaning of this project in a political setting and future research are reflected upon.

6.1 Statement of principal findings

The results show that the costs of producing one incremental QALY for patients suffering AIS are DKK 224,146.62.

Due to the assumptions made, the results are associated with uncertainties and therefore sensitivity analyses were performed. These show that the most influential parameters on ICER are several utility values and risk of recurrence in the 'no treatment strategy' branch. Furthermore, there is a 7.2% risk that the treatment of AIS can produce a negative incremental effect.

6.2 Strengths and weaknesses of the study

6.2.1 Population

Patients suffering AIS was chosen as the population because AIS is the third-most-expensive disease to treat, and that treatment results in the second-highest QALY gain out of multiple diseases[10]. The most expensive disease to treat is cancer[10]. However, since the QALY gain of treating cancerous diseases is low, this could result in an unreasonably high ICER, and as a result cancer was deselected in favor of AIS. It could be argued that patients suffering AIS do not represent the entire population since mainly the elderly suffer from AIS[12]. This could lead to lower costs and lower QALY compared to diseases affecting the young, considering these QALYs would accumulate over more years. Nevertheless, AIS is believed to be representative of the health-care system because the disease is common and both QALY gain and costs are rated somewhat equal[10].

An advantage of choosing AIS is the many types of treatment offered to patients. Treatment includes acute pre-hospital care, surgeries, short- and long-term admissions, rehabilitation, home care, and daily medication intake. This was seen as an advantage for this project as it reflects the complex health-care system in Denmark.

6.2.2 Structure of the Markov model

A Markov model was used to estimate the costs of producing one incremental QALY in Denmark. The strength of using a Markov model is the possibility to create an intuitive simplification of the real world. However, this could also be perceived as a weakness because the real world is more complex than a model can encompass.[5] Therefore, *"all models are wrong, but some are useful"*[56]. The model in this project is not exhaustive because it does not account for any adverse events, which is a downside since it is implausible that zero patients would experience adverse events. The most common adverse event after treatment of AIS is intracranial hemorrhage (ICH), which approximately 4.4% of patients will incur[34].

ICH was left out of the model because it is a complex disease area with opposing treatment guidelines compared to AIS. This could be included by adding one-time costs and utility-loss in TreeAge Pro as the transition occurs. However, if ICH or other adverse events should be included it would be necessary to build an entirely different and very large model, which is beyond the scope of this project. Despite the exclusion of adverse events, the probability of patients suffering recurrence is included in the model. This probability does not differ between mRS-states since this was not differentiated in the included studies. Therefore, it is assumed that the probability of suffering recurrence is the same in all mRS-states. Recurrence is included to complete the progression of AIS.

Different assumptions were made for simplification of the model. For example, it is assumed that patients cannot remit, even though this would be unlikely[18; 57]. According to the tornado analysis (see section 4.2.1.1), the probability of remission is one of the most influential parameters on the result. The assumption was necessary because data on the probability of remission was not available. The authors are aware that this assumption might be incorrect, nevertheless, it was verified by a clinical expert and inspired by previous Markov models [23; 40; 58] and is therefore believed to be legitimate.

6.2.3 Estimation of health utility values

Health utility values were found through a systematic literature search leading to an article by Ali et al.(2016), where health utility values are estimated using Danish EQ-5D-3L weights[36]. This is a strength since utility weights are not necessarily the same across different countries[59]. Furthermore, the weights are applied to a rather large population of 3827 indicating high confidence in the results[60].

Health utility values are assumed to be constant for all 120 cycles, which is validated partially by the literature and partially by the clinical expert[12; 40]. The utility value for each mRS-state is estimated at three months after initial AIS. However, it might be worth

considering that these values could change over time even though the patient remains in the same mRS-state. Either because the patients learn to cope with the functional impairment or - on the contrary - because the health utility value decreases over time as the patient realizes the impairment is permanent. A Spanish study by Luengo-Fernandez et al.(2013) shows increasing utility values for patients suffering severe stroke from one month to 24 months, followed by a decrease. On the other hand, patients suffering minor stroke have stable utility until 12 months followed by a decrease in utility until 60 months. The study includes both ischemic and hemorrhagic stroke and does not differentiate between different mRS-states.[61] These fluctuations in utility values could indicate that the assumption made in this project is not correct and that utility values are not constant over time. Nevertheless, Danish treatment guidelines and the clinical expert verified the assumption and thus the assumption was included in the model. Utility values in the article by Luengo-Fernandez et al.(2013) seem to change the most between one and six months and then flatten out[61], which could also support the assumption that utility values become constant over time. This could be included for future research, by conducting long-term studies investigating changes in mRS-states following AIS.

6.2.4 'Current treatment strategy'

For the 'current treatment strategy' branch, a thorough and systematic literature search was performed and the quality of relevant articles was assessed using GRADE and PRISMA checklists. This is a strength since quality of the articles was considered and led to exclusion of articles. Even though all relevant articles were assessed, not all included articles were rated *high* e.g. the articles by Stahmeyer et al.(2019) and Ciccone et al.(2013) that do not differentiate between treatments[35; 37]. Use of these data could be a drawback since it might not be transferable to our population. These data were not applied to the model without thought and deliberation, but no exact data were found. Furthermore, uncertainty on these values was investigated in the sensitivity analyses, showing that parameters extracted from these studies do not have a large impact on the result.

6.2.5 'No treatment strategy'

In the 'no treatment strategy' branch it was necessary to make a great deal of assumptions on the grounds that no literature existed providing values for the parameters. Instead, we consulted a medical doctor and expert in stroke to get these probabilities. This is a weakness because expert opinions are rated *low* in the hierarchy of evidence, whereas RCTs and systematic reviews are rated *high*[31]. On the other hand, the medical doctor consulted for this project, is one of the leading research scientists in this field in Denmark. The authors acknowledge the weakness in this way of estimating parameters and investigate uncertainty in the sensitivity analyses.

The mRS-states were grouped to make outcome estimations simpler. The utility values applied to the model are the same as the 'current treatment strategy' branch, but the lowest utility value for each group was used. This could result in an under- or over-estimation of QALY, however, the low values were chosen to reflect the fact that a patient receiving no treatment or care would presumably have a lower health utility score than a patient receiving treatment. The actual utility values associated with the 'no treatment strategy' branch would be practically impossible to investigate using e.g. EQ-5D or VAS because a cessation of treatment is both unlikely and unethical.

6.2.6 Costs

Estimation of costs related to treating AIS is based on cost data from different sources. For instance, DRG-rates used for hospitalization costs are averages from the five Danish Regions and do not reflect exact costs. This could lead to the applied costs being either too high or too low compared to the actual costs. However, the rates used in this study are based on data from the previous year and then extrapolated and adjusted for inflation and salary changes. This way of estimating the DRG-rates is an advantage seeing that this project aims to estimate the average costs of treating AIS in the entire country.

Rehabilitation costs were estimated using DRG-rates as well. A large uncertainty on rehabilitation exists, since the duration and need for constant care is individual to each patient. Furthermore, the DRG-rates do not consider the specific disease and therefore the costs for AIS could be either higher or lower than the average. To account for uncertainty on DRG-rates, a PSA was performed which is a recognition of these uncertainties and an asset to this project.

The authors were in contact with the Danish Regions to obtain exact treatment costs, but these costs were unavailable.

6.2.7 Sensitivity analyses

Essentially, sensitivity analyses are an advantage due to the recognition of uncertainties. By doing both deterministic and probabilistic sensitivity analyses we acknowledge uncertainty surrounding the estimates and assumptions included in the Markov model. A strength of this project is the use of multiple sensitivity analyses to investigate both methodological and parameter uncertainties.

6.3 Strengths and weaknesses in relation to other studies

The literature search showed no previous studies investigating the costs of producing one incremental QALY in Denmark. However, some studies investigate the cost-effectiveness of AIS treatment using Markov models. Lobotesis et al.(2016) compared two treatment

strategies for AIS. They applied probabilities of patients remitting and progressing in the rehabilitation phase after initial AIS.[23] The probabilities from the study are extracted from an RCT by Jung et al.(2011) investigating basilar artery occlusion, which is one of several subtypes of AIS, and had a very small population[57]. The study was not transferable to the population in this project and therefore excluded.

Kunz et al.(2018) also validated the assumption that no patients remit or progress, and assume no significant improvement in mRS-state after three months[58]. They extract age-dependent probabilities on mRS-states from Goyal et al.(2016), the meta-analysis used in this project. Future research could investigate age-dependent probabilities of mRS-states after initial AIS, considering the likelihood of younger patients ending in a better mRS-state is higher than older patients[58].

Using mRS as health states in the model is previously done in other CEAs of AIS treatments[23; 58; 62]. This is a strength of this project, since costs of patients ending up in different mRS-states are assigned each state, and there is a great difference in costs of patients ending up in mRS0 and mRS5. By building health states corresponding to mRS-states it is possible to differentiate costs of rehabilitation in the model. A study by Ehlers et al.(2007) estimated the cost-effectiveness of implementing tPA in Denmark and also used mRS-states[62]. These data were not used in this project because they were estimated 14 years ago and an extrapolation would probably not provide the right treatment costs because of changes in the way AIS is being treated, e.g. EVT was implemented in 2018 as standard treatment[63].

6.4 Meaning of this project: possible mechanisms and implications for policymakers

As a result of the decision to implement QALY as an effect measure it is interesting to investigate the costs of producing one incremental QALY as a way to assess opportunity costs. Furthermore, it should be considered how to use QALY as a tool for decision-making when evaluating new treatments. As of now, no official CET exists in Denmark[4] and it seems highly unlikely that this would change in the near future - primarily because *"putting a price on human life"*[64] is an unpopular opinion amongst both politicians and the general public.

The results of this project could help DMC in making decisions about whether or not to implement new interventions based on price per QALY. However, the ICER results should and will in all probability never stand alone when making decisions, but as the decision should also include considerations about severity, caution, and rarity[3]. An estimation of the costs of producing a QALY in Denmark has to the authors' knowledge not been done

before but could aid in decision-making. We have not tried to - nor do we intend to - put a price on human life, but wish to help provide maximum health gain for the resources available.

6.4.1 The need for prioritization

Across the world, prioritization is a fundamental challenge in health-care[5; 65]. A continuous increase in health-care expenses will increase pressure on the Danish economy. Contributors to the increasing costs are expensive treatment regimens, an aging population, higher living standards and scientific innovations.[10; 66] This results in higher expectations from patients to treatment and health services in general. A problem is the high costs of new treatments, which is not necessarily a reflection of an increase in effect.[66]

Scarce resources and a finite budget require considerations about prioritization of e.g. labor, personnel, time, education, medication - and especially new and very expensive interventions cause problems[5; 66]. Regardless of the indisputable importance of prioritization in health-care, this topic is not popular among politicians despite the fact that health-care professionals do prioritize on a daily basis[1]. However, the choice to not prioritize explicitly is also a choice, but an unjust one. Instead of an attempt to distribute the resources in a way to produce the most possible welfare, the choice is simply not made by the responsible authorities.[5; 6; 67] We therefore strongly encourage politicians and decision-makers to reconsider the choice to not prioritize in health-care in Denmark.

A method that can be used as an aid in prioritization is setting a CET.

6.4.2 Setting the appropriate cost-effectiveness threshold

A CET is necessary if one wishes to determine whether an alternative is cost-effective or not. A fixed CET will aid in decision-making.[5] However, if a CET is not explicit due to e.g. political reasons, it would be an advantage if the companies applying for approval of new interventions believed the CET was low. Even though a threshold would be implicit, this could put pressure on the companies to lower their prices if they believe the CET is reasonably low.

Baker et al.(2011) argue that a CET can be based on two approaches, that are methodologically different: 1) an opportunity cost approach and/or 2) a WTP-approach, also known as a supply-sided approach and a demand-sided approach, respectively. The two approaches should be considered as complementary and not as rivals or competitors like

[1] Quotes from politicians in the book "Prioritering i sundhedsvæsenet" by Kjeld Møller Pedersen(2015)[67], translated from Danish: "*In a wealthy society, as the Danish society, we should be able to afford...*", "*You cannot put a price on human life*", and "*Only the best is good enough - no matter the price*".

previously.[68] It is an ongoing discussion whether to use WTP or opportunity cost as a basis for estimating a CET[65; 68; 69; 70].

The main theoretical issue with a WTP-based threshold is that this does not reflect a finite budget with scarce resources. Thereby, it does not reflect opportunity costs. The consideration of where the resources are used at their optimal value is not incorporated in WTP.[65; 70]

6.4.2.1 Opportunity cost/supply-sided approach

The opportunity cost approach - also known as the supply-sided approach - is based on the principle of scarce resources. In any society, the resources are scarce, which puts an upper limit to the size of its health-care budget. Unless a new intervention is cheaper than the current, implementation requires additional resources, which results in a displacement of resources and savings in other areas of the health-care sector, or, ultimately, in other parts of society. As per this approach, a CET should represent the value of the QALY you are giving up when implementing a new intervention.[68; 71]

Below is a purely hypothetical example explaining the relevance of using opportunity costs for estimating CET:

> *If a new intervention, called A, can contribute with a QALY gain of 10 QALY per patient for the costs of DKK 10,000,000 this would give a price of DKK 1,000,000 per QALY. If these costs are not compared to anything, it is difficult to tell whether the costs are too high or fair. However, if the costs per QALY are compared to the ICER from this project of DKK 224,146.62 per QALY, then DKK 10,000,000 could buy approximately 45 QALYs in the treatment of AIS. The difference between implementing intervention A and treating patients suffering AIS is called opportunity costs. If A was implemented instead of treatment of AIS, this could mean a loss of 35 QALY. This way of using an opportunity cost approach tells us that implementing intervention A would result in a loss in welfare.*

The opportunity cost approach is taken in the current project and this approach is seen as the gold standard for estimating CETs[5; 9; 72].

6.4.2.2 Willingness-to-pay/demand-sided approach

Willingness-to-pay (WTP) is a technique used for putting a monetary value on health effects. Traditionally, two techniques are used for this: revealed and stated preferences. Revealed preferences are used as an approach in economics to understand the valuation of different goods by e.g. investigating the amount previously paid for a certain good.[5; 6]

When using stated preferences to investigate WTP, respondents are presented with hypothetical scenarios and asked to chose or comment on this. An example of stated preferences is discrete choice, where respondents are asked to chose which of two health states they prefer. Later, they are asked to chose how much they are willing to pay for their preferred health state. Another example is contingent valuation, where respondents are asked how much they are willing to pay to maintain a specific health state. [5; 6]

One of the challenges of using WTP to estimate CET is that there is a difference between individuals' income, which also results in a difference in ability-to-pay (ATP). The higher the income, the more an individual is willing to pay for an increase in health.[69] Due to this and because the general public does not have the expertise to aid in decision-making, it is not favorable to base CET on the population's WTP.[65; 69]

Claxton et al.(2015) argue that basing a CET on WTP does not help decision-makers decide how to allocate the budget, as it does not account for a finite budget, but assumes the budget can adapt[72]. Furthermore, it might be a problem that some diseases are perceived more severe than others by the public. In Denmark, cancer is one of the most covered diseases in the media with so-called cancer-weeks, televised fund-raising events, and a large political backing. If a cancer-scenario was compared to e.g. chronic obstructive pulmonary disease (COPD), public respondents would probably rate cancer higher - even though this might not reflect the actual change in HRQoL.

Contrarily, some ethicists argue that it is irresponsible to not include an estimation of WTP by the public since governments should act according to society's priorities. They argue, that surely the population's values and opinions should be included in decision-making since they are part of the society.[73]

6.4.3 Ethical considerations

When talking about prioritization, a talk about ethics is inevitable. Fair prioritization is about allocating resources in a way that ensures all patients the greatest possible health gain. The Danish Health Act states that all citizens have equal rights to health-care, however, some diseases are given lower priority than others. For example, COPD and schizophrenia have low priority while cancer has a higher priority.[10] Some argue that patients responsible for their disease due to bad lifestyle choices, such as COPD, should have a lower priority.[10; 74] This would violate the principle of justice and the fact that all patients should be treated equally[10].

The Danish Council on Ethics states that the use of QALY can lead to fair prioritization between different groups of patients[10].

6.5 Comparison with threshold values in other countries

6.5.1 The United Kingdom

The United Kingdom is the only country with an official CET for a QALY. The threshold value is empirically based on very limited evidence, however, it seems to lean on previously accepted interventions.[72] The CET is between GBP 20,000-30,000 per QALY corresponding to DKK 176,400-264,600 per QALY[2], but NICE is known to have accepted treatments with an ICER of GBP 50,000 per QALY for life-extending end-of-life treatments.[67; 75] The ICER in this project of DKK 224,146.62 per QALY matches the NICE guidelines of WTP per QALY by being in the middle.

6.5.2 Norway

In Norway, no official CET for QALY exists. Nonetheless, in 2015 Norway evaluated the relationship between loss of QALY and WTP. The lower boundary of WTP was NOK 275,000 per QALY corresponding to DKK 209,000[3], but can increase up to NOK 825,000 per QALY depending on the QALY gain. The lowest category of QALY gain inlcudes 0-3.9 QALYs gained[76]. The estimation of NOK 275,000 per QALY is based on NICE's GBP 20,000 per QALY threshold and then raised a bit[77]. Results from this project show an incremental QALY of 3.67, which would place AIS in the lowest of 6 categories corresponding to a WTP of 209,000 DKK. This is somewhat in accordance with the ICER in this project, which could implicate that the results are useful in a decision-making context.

6.5.3 Sweden

The Swedish parliament, Riksdagen, has decided to prioritize based on four principles; severity of the condition, effect size, the certainty of results, and the rarity of the disease. This means that CET can differ between different conditions.[78] Siverskog et al.(2019) estimated the costs for a marginal life year in Sweden to SEK 370,000 corresponding to approximately DKK 263,000. However, these calculations did not account for HRQoL, only life years, and can therefore not be translated directly to a CET for QALY. They use an opportunity cost approach and argue that this is the most respected way to estimate a CET.[9]

[2]Because of the ongoing COVID-19 pandemic the value of a Pound sterling decreased significantly, and an exchange rate of 8.82 from January 2020 was chosen.

[3]Because of the ongoing COVID-19 pandemic the value of a Norwegian krone decreased significantly, and an exchange rate of 0.76 from January 2020 was chosen.

6.5.4 Gross domestic product per capita

Previously, the WHO suggested using three times the gross domestic product (GDP) per capita as a CET per averted disability-adjusted life year (DALY). Originally, this was only recommended for DALY but was later expanded to include QALY as well. Only one country, Poland, is known to use this CET for QALY.[65; 69; 79] This approach of estimating CET is a WTP/demand-sided approach and does not consider opportunity costs. In Denmark, the average GDP per capita is DKK 398,900 giving a CET of approximately DKK 1.2 million, which is 5.3 times higher than the ICER from this project. This could indicate that either the ICER from this project or the GDP per capita-approach would never be used as a CET. The advice from the WHO to use GDP per capita is based on an article by the WHO-CHOICE task force published in 2003[79]. This could be argued to be out-of-date in a 2020-setting taking into account that plenty of research and advances in the field of health economics have been made since then.

6.5.5 Recent work of estimating a cost-effectiveness threshold

As mentioned above, the NICE CET is not based on opportunity costs, but on revealed preferences. Claxton et al.(2015) attempt to estimate the CET based on opportunity costs in the National Health Service (NHS). This is done by comparing various budgets of the NHS to the overall mortality and translate this into QALY gain or loss.[72] The benefit of this way of estimating a CET is the consideration and estimation of opportunity costs in order to investigate in which field the NHS can produce the highest amount of welfare for the available resources.

An opportunity cost approach is likewise taken in this project, although on a smaller scale and with another method for estimating the opportunity costs. In this project, the opportunity costs are estimated by investigating a specific disease area in detail. This is both a strength and a weakness, since the estimations are based on precise data, but only one disease is investigated. To our knowledge, this methodology has not been applied before. For further research, it could be both interesting and relevant to broaden this methodology and investigate other disease areas.

6.6 Unanswered questions and future research

AIS is a disease with high costs and a potentially high QALY gain whereas other diseases such as allergy and tinnitus are associated with low costs and low QALY gain[10]. For future research, it could be interesting to investigate the costs of producing one incremental QALY in other disease areas. To get a more exact estimate of costs of producing one incremental QALY, a less costly disease area with a higher QALY gain such as the

orthopedic area or the area of childbirth could be investigated. The orthopedic area is known to be extremely efficient, whereas the area of childbirth potentially produces a very high QALY gain.

As an example, a Danish CEA by Skou et al.(2020) concludes that total knee replacement compared to non-surgical treatment gives an ICER of approximately DKK 138,000 per QALY[80]. This along with other examples show that disease areas have different ICER values[10]. It might also be worth noting that optimization and streamlining are simply easier for some diseases than others. An example of this is orphan diseases with a prevalence of maximum 1-2/10,000[81], where streamlining is extremely difficult because of few patients. Regardless, these patients should undoubtedly receive treatment despite high costs per QALY[10]. In the United Kingdom, NICE is willing to raise the recommended threshold limit to GBP 80,000 (see section 6.5.1) and in Norway, the recommended threshold can be raised up to 19 times [75; 82]. If a CET was applied in Denmark, a higher CET for orphan diseases should also be considered. Furthermore, medical interventions for orphan diseases are difficult to assess using QALY because clinical evidence of effect might be limited due to few patients.

An investigation of a way to weight QALY gain could also be an interesting topic for further research. Even though it is assumed that all QALYs are valued equally, a marginal QALY might be worth more for individuals having few QALYs, than individuals with many QALYs in sight[83]. Furthermore, patients that have suffered a specific disease might rate this lower than patients not having suffered from that disease. Therefore it would be interesting to weight marginal QALY depending on e.g. the recipients' age or utility before an intervention.

6.6.1 The COVID-19 pandemic

Recently, the COVID-19 pandemic forced not only Denmark but the entire world to introduce lock-down measures to reduce the spread of the deadly virus and prevent a collapse of health-care sectors. The pandemic forced the Danish government to prioritize in all sectors and especially in the health-care sector. As of May 2020, the average welfare loss in the Danish health-care sector per month is estimated to DKK 2.5 billion. For this amount of money, approximately 2,000 COVID-19 related deaths are avoided and there is a risk that the cure costs more than an actual disease outbreak would amount to.[84] The statements made by health economics professor Jakob Kjellberg indicate a societal WTP of DKK 1,250,000 per death avoided, which seems unreasonably high compared to other CETs and ICERs. The opportunity costs of doing this are high, considering that for instance the costs of producing one QALY in the disease area of AIS are "only" DKK 224,146.62.

Nonetheless, the government sends out a clear signal, that they are not willing to put

a price on human life. On the other hand, the authors - as aspiring health economists - hope that both the government and the general public begin to reflect not only on the costs of avoiding this disease, but also on the costs of treating other diseases, even though the act of prioritizing in the health-care sector is frowned upon. Hopefully, it becomes clear that a lock-down leading to postponed treatments in other areas of the health-care sector is also a way of prioritizing. This gives reason to expect that prioritizing in the health-care sector will gain recognition in the near future in order to provide most welfare for the scarce resources available.

Chapter 7

Conclusion

Based on the results from the Markov model, the costs of producing one incremental QALY for patients suffering AIS is DKK 224,146.62. This should not be seen as a CET, but as an estimation of opportunity costs.

The result is associated with uncertainties because of the assumptions made. Deterministic sensitivity analyses were performed to show the most influential parameters and that adding cost of nursing homes would change the ICER to DKK 281,793.74 per QALY. The uncertainties were furthermore investigated in a PSA showing that there is a large uncertainty surrounding the results.

Further research is needed to gain greater insight into the costs of producing one incremental QALY in Denmark to assess opportunity costs. This could be done with the same approach as in this project by investigating other less costly diseases, orphan diseases or diseases with a higher QALY gain.

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Appendix A

Abstract - Danish

Formål: Formålet med opgaven er at estimere omkostsningerne ved at producere et inkrementelt kvalitets-justeret leveår (QALY) for patienter med akut iskæmisk apopleksi i Danmark. Dette kan bruges til at vurdere alternativomkostningerne i den danske sundhedssektor.

Metode: En Markov model bruges til at estimere omkostninger i DKK og effekt i QALY af to alternativer, hvoraf det ene afspejler den nuværende behandlingsstandard og det andet afsplejer et hypotetisk scenarie, hvor sygdommen ikke behandles. I analysen tages et begrænset samfundsperspektiv og parametrene til modellen bliver primært fundet gennem flere systematiske litteratursøgninger.

Resultat: Resultaterne viser, at omkostningerne ved at producere en inkrementel QALY i Danmark er DKK 224.146,62. På grund af antagelser er der dog usikkerheder forbundet med dette estimat.

Diskussion: Først diskuteres de metoder, der er blevet brugt til at estimere omkostninger og effekt af alternativerne. Dette efterfølges af en sammenligning af denne opgave med lignende studier. Størstedelen af diskussionen omhandler vigtigheden i at prioritere i sundhedssektoren og måder hvorpå en tærskelværdi for omkostningseffektivitet kan estimeres.

Konklusion: Omkostningerne ved at producere en inkrementel QALY i Danmark er DKK 224.146,62. Fremtidig forskning bør tage udgangspunkt i at undersøge andre sygdomsområder, så alternativomkostningerne i det danske sundhedsvæsen kan blive estimeret.

Appendix B

Current practice of prioritization in Denmark

In 2017, the Danish Regions established the Danish Medicines Council (DMC).

B.1 The Danish Medicines Council

DMC evaluates new treatments and compares them to existing standard treatments based on e.g. longer lifetime, less adverse events, and increased quality of life (QoL). Based on assessments from health care professionals, treatments are placed on a scale of five categories showing the added clinical benefit.[85] The five categories are inspired by the German Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG):

- Great added clinical benefit
- Important added clinical benefit
- Small added clinical benefit
- No added clinical benefit
- Negative clinical benefit
- Non-documentable added clinical benefit
- Added clinical benefit of unknown magnitude [85]

DR is willing to pay more for a new treatment with great added clinical benefit than treatments with low clinical benefit[1]. Not only added clinical value determines if a new treatment should be implemented, but adverse effects and QoL is also considered[86]. Following the assessment of added clinical benefit, DMC evaluates the costs of treatment. DMC evaluates new medicine and indications for existing medicine and develops treatment guidelines for therapeutic areas.[1]

The Danish Parliament uses seven principles for prioritization of medicine in Danish hospitals, that are followed by the DMC. The principles are:

A Professional competence

B Independence

C Geographic equality

D Transparency

E Rapid uptake of new, effective medicine

F More value for money in health

G Access to treatment[87]

In November 2019, DR decided that DMC shall evaluate new treatments using QALY as an effect measure. Initially, the QALY-method should be implemented in October 2020, but because of the COVID-19 pandemic, this is postponed 6 months[2].

B.2 Amgros I/S

Amgros I/S is an organization providing public hospitals in Denmark with the right treatment at the right price at the right time. They negotiate prices on medicine based on clinical benefit provided by the DMC and cost-analyses provided by pharmaceutical companies and DMC.[1] Furthermore, Amgros I/S cooperates with hospital pharmacies in all five regions and have the authorization to produce 65 different medicines in case of a national or international emergency.[88]

Appendix C

Literature search - search protocol

Master's Thesis - MMA

Table of Contents

Topic

Names: Cecilie Astrup Frederiksen, Matilde Slot
Group: 20gr10025
Supervisor (main): Lars Holger Ehlers

Title:	An estimation of the costs of producing an incremental QALY for patients suffering acute ischemic stroke in Denmark
Aim:	The aim of this project is: to estimate the costs of producing one incremental QALY for patients suffering acute ischemic stroke in Denmark. Two scenarios will be compared in a Markov Model. One scenario reflecting the cur-rent treatment strategy, and the other reflecting a no treatment strategy with no healthcare sector at all. These are compared because the aim is to estimate the value of an incremental QALY, and not just a QALY. In a primary analysis, a limited societal perspective including all relevant costs related to hospitalization, home care and out-of-pocket payments is investigated. As secondary analyses, a societal perspective and a health-care payer perspective is chosen to reflect other scenarios.

Master's Thesis - MMA

Search strategy

Database/source of information	Reason for choice
Embase	One of the biggest, medical databases. The controlled search term is called EmTree.
PubMed	One of the biggest, medical databases. Includes MedLine and York database of HTA. The controlled search term is called MeSH.

Limitations (Exclusion/Inclusion)

Database	Limitation	Reason
PubMed, Embase	Disease "stroke"	Must be acute ischemic stroke. Excluded if intracranial hemorrhage and transient ischemic stroke. - Other neurovascular diseases are also excluded
PubMed, Embase	Language	English or Danish due to understanding
PubMed, Embase	Country	Some countries were excluded due to low comparability to a Danish setting. The excluded countries were e.g. Nigeria, Tanzania and other developing countries.
PubMed, Embase	Study type	Filters were added to secure the highest level of evidence from the hierarchy of evidence. Systematic-reviews, meta-analysis and randomized controlled trials were preferred.

B

Master's Thesis - MMA

Health utility values

PubMed

Date: March 12th, 2020

	AND		
	Disease (stroke)	Quality of Life	Modified rankin scale
OR	Stroke (MeSH) Ischemi* stroke (free text)	Quality of Life (MeSH) Patient Reported Outcome Measures (MeSH) Quality-Adjusted Life Years (MeSH) Utility (free text)	Modified Rankin Scale* (free text) mRS (free text)

Embase

Date: March 12th, 2020

	AND		
	Disease (stroke)	Quality of Life	Modified rankin scale
OR	Brain Ischemia (EmTree) Ischemic stroke (free text)	Quality of Life (EmTree) Patient-Reported Outcome (EmTree) Quality adjusted life year (EmTree) Utility (free text)	Modified Rankin Scale (free text) Rankin Scale (EmTree) mRS (free text)

C

Master's Thesis - MMA

Results

PUBMED - UTILITY		NUMBER OF HITS
1	"Stroke"[Mesh]) OR (("ischemia"[MeSH Terms] OR "ischemi*"[All Fields]) AND ("stroke"[MeSH Terms] OR "stroke"[All Fields])	141,011
2	"Quality of Life"[Mesh] OR utility OR "Quality-adjusted life years"[MeSH] OR "Patient Reported Outcome Measures"[Mesh]	390,899
3	(modified[All Fields] AND rankin[All Fields] AND "scale*"[All Fields]) OR mRS	28,352
4	1 AND 2 AND 3	273
5	FILTER: Language English or Danish	261

EMBASE - UTILITY		NUMBER OF HITS
1	'Brain ischemia'/exp OR 'ischemic stroke'	228,184
2	'Quality of Life'/exp OR utility OR 'quality adjusted life year'/exp OR 'Patient-Reported Outcome'/exp	747,876
3	'Rankin scale'/exp OR 'Modified Rankin Scale' OR mRS	56,852
4	1 AND 2 AND 3	644
5	FILTER: Language English or Danish	631

D

Master's Thesis - MMA

Transition probabilities

PubMed

Date: March 19th, 2020

	AND		
	Disease (stroke)	Outcome probability	Modified rankin scale
OR	Stroke (MeSH) Ischemi* stroke (free text)	Outcome Assessment, Health Care (MeSH) Probability (MeSH) AND Treatment type: Thrombolytic therapy (MeSH) Thrombectomy (MeSH) Embolectomy (MeSH) Platelet Aggregation Inhibitors (Mesh) Clopidogrel (MeSH) Aspirin (MeSH)	Modified Rankin Scale* (free text) mRS (free text)

Embase

Date: March 19th, 2020

	AND		
	Disease (stroke)	Outcome probability	Modified rankin scale
OR	Brain Ischemia (Emtree) Ischemic stroke (free text)	Risk (Emtree) Probability (Emtree) Outsome assessment (emtree) AND Treatment types: Fibrinolytic therapy (Emtree) Thrombectomy (Emtree) Embolectomy (Emtree)	Modified Rankin Scale (free text) Rankin Scale (Emtree) mRS (free text)

E

		Antithrombolytic agent (Emtree) Clopidogrel (Emtree) Acetylsalicylic acid (Emtree)	

Results

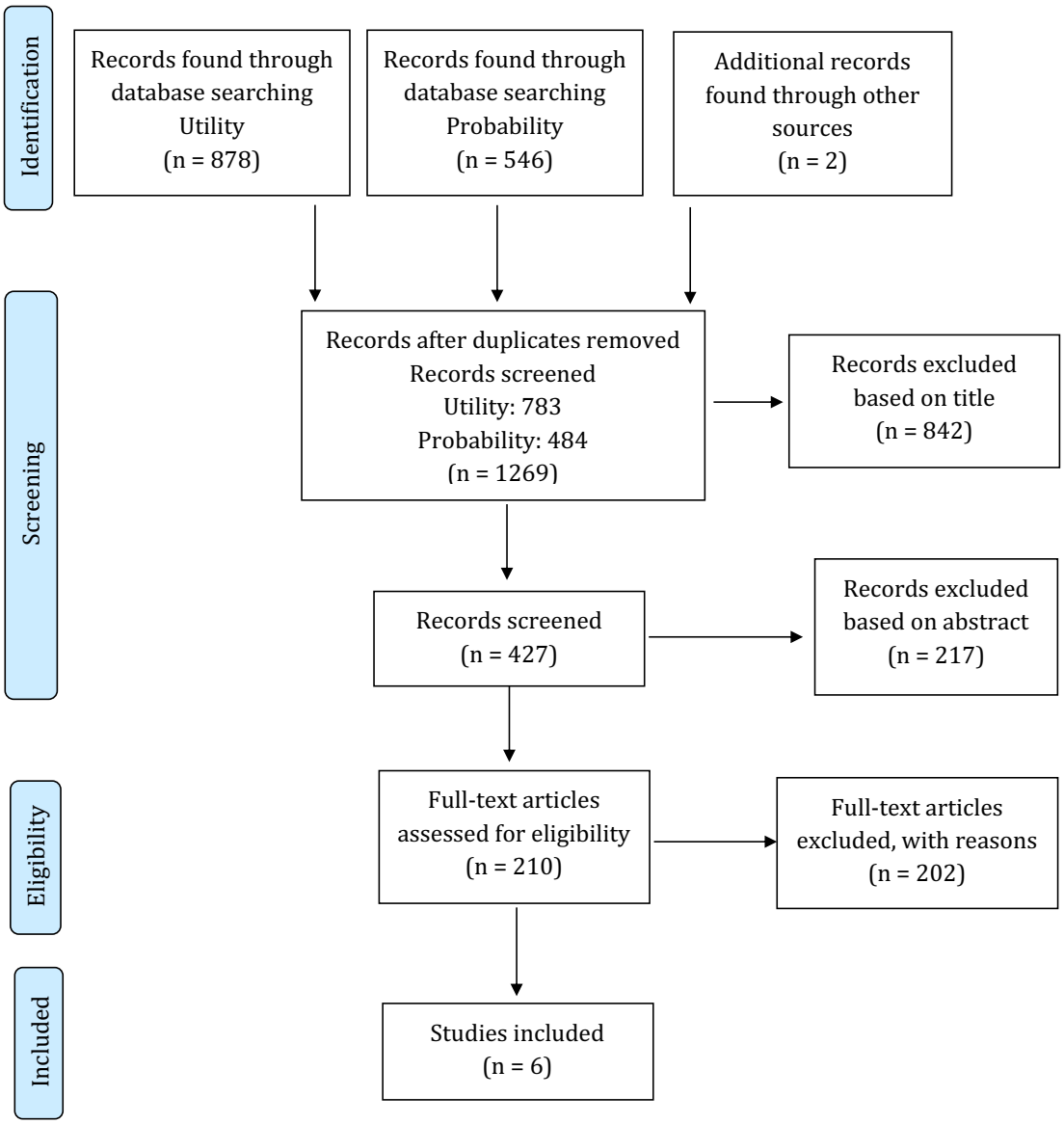
PUBMED - Transitions		NUMBER OF HITS
1	"Stroke"[Mesh]) OR (("ischemia"[MeSH Terms] OR "ischemi*"[All Fields]) AND ("stroke"[MeSH Terms] OR "stroke"[All Fields])	141,434
2	("Probability"[Mesh]) OR "Outcome Assessment, Health Care"[Mesh]	2,286,894
3	(((((("Thrombolytic Therapy"[Mesh]) OR "Aspirin"[Mesh]) OR "Embolectomy"[Mesh]) OR "Thrombectomy"[Mesh]) OR "Clopidogrel"[Mesh]) OR "Platelet Aggregation Inhibitors"[Mesh]	99,959
4	(modified[All Fields] AND rankin[All Fields] AND "scale*"[All Fields]) OR mRS	28,444
5	1 AND 2 AND 3 AND 4	1633
6	FILTER: Language English or Danish Article types: Meta-analysis, systematic review, randomized controlled trials	300

EMBASE - Transitions		NUMBER OF HITS
1	'Brain ischemia'/exp OR 'ischemic stroke'	228,568
2	'Risk'/exp OR 'probability'/exp OR 'outcome assessment'/exp	2,925,536
3	'fibrinolytic therapy'/exp OR 'thrombectomy'/exp OR 'embolectomy'/exp OR 'antithrombocytic agent'/exp OR 'clopidogrel'/exp OR 'acetylsalicylic acid'/exp	388,708
4	'Rankin scale'/exp OR 'Modified Rankin Scale' OR mRS	56,962
5	1 AND 2 AND 3 AND 4	1600
6	FILTER: Language English or Danish Article type: meta-analysis, systematic review, randomized controlled trials	246

F

Master's Thesis - MMA

PRISMA 2009 Flow Diagram:



G

Appendix D

Results of quality of evidence

D.1 Ali et al.(2016) - utility values

Author	Risk of bias	Inconsistency	Indirectness	Imprecision	GRADE
Ali et al.(2016)	↑	—	↑	↑	Moderate

Table D.1: GRADE of observational study by Ali et al.(2016)[36] used to present utility values for each mRS-state. —: No reason to upgrade, ↑: reason to upgrade.

Author	Ali et al. (2016)
Risk of bias	Low risk. The study is upgraded.
Failure to develop and apply appropriate eligibility criteria	*Low risk*
Flawed measurement of both exposure and outcome	*Low risk. Use of country-specific EQ-5D-3L preference weights to calculate utility.*
Failure to adequately control confounding	*Unclear*
Incomplete or inadequately short follow up	*Low risk. Most studies made in the stroke-area use a 3-month follow up, which is also done by Ali et al.*
Inconsistency	"Age and initial stroke severity by NIHSS were largely comparable across countries having a sample size of more than 50 patients."
Indirectness	The study includes a Danish population-based on the VISTA-database. The study is upgraded.
Imprecision	Large study population and reliable use of health utility value sets. The study is upgraded.
GRADE	Moderate

Table D.2: Detailed description of GRADE for Ali et al.(2009)[36]

D.2 Goyal et al.(2016) - probability of mRS-states

D.2.1 PRISMA checklist

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1-2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	1-2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	NA
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	NA
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	NA
Own comments:		The aim of the study was to compare five randomized controlled trials and not to identify literature on the subject. Therefore, it is accepted that the meta-analysis lacks information about a literature search.	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Appendix
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Appendix
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	NA
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	3

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I_2) for each meta-analysis.	3

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	4 Appendix
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	NA
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Appendix
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6 Appendix
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	5
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	5 and 6
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	6 and 7
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	4

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097.

D.2.2 GRADE

Author	Name of study	Risk of bias	Inconsistency	Indirectness	Impresicion	GRADE
Berkhemer et al. (2015)	MR CLEAN	—	—	—	—	High
Jovin et al. (2015)	REVASCAT	—	—	—	—	High
Campbell et al. (2015)	EXTEND IA	—	—	↓	—	Moderate
Saver et al. (2015)	SWIFT PRIME	—	—	—	—	High
Goyal et al. (2015)	ESCAPE	—	—	—	—	High

Table D.3: Classification of trials used to provide transition probabilities for mRS-states after three months. All studies are included in [34]. —: no reason to downgrade, ↓: reason to downgrade.

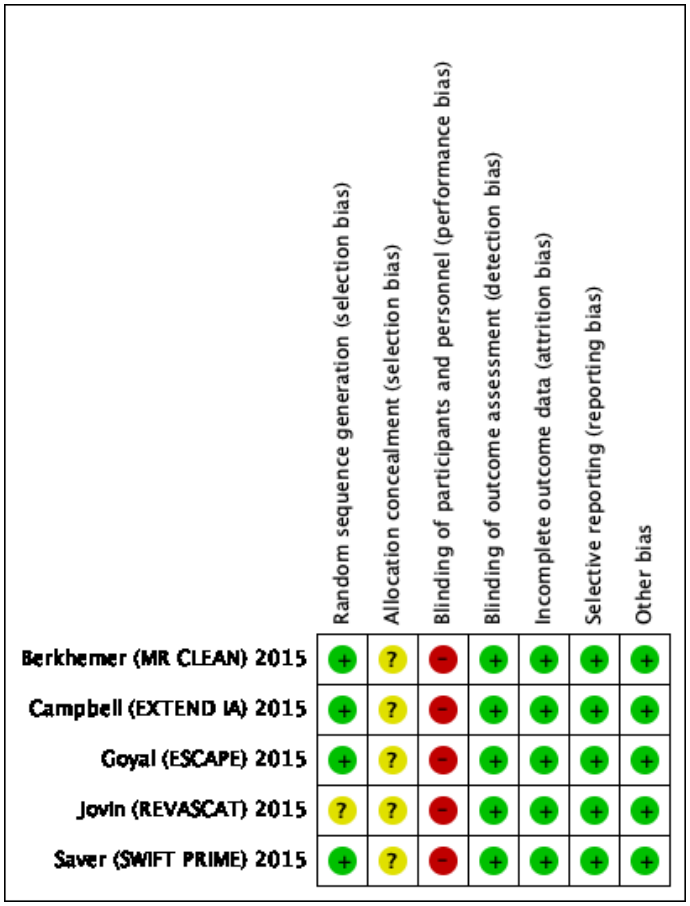


Figure D.1: Risk of bias for the five included studies in the meta-analysis by Goyal et al.(2016)[34].

None of the trials are double-blinded because tPA is administered intravenously and EVT is a surgical procedure. Collection of outcome data for treatment was collected by an external, blinded assessor.

D.3 Ciccone et al.(2013) and Stahmeyer et al.(2019) - recurrence of stroke

Author	Risk of bias	Inconsistency	Indirectness	Imprecision	GRADE
Ciccone et al.(2013)	—	↓	↓	—	Low
Stahmeyer et al.(2019)	↑	—	—	↑	Moderate

Table D.4: Rating of studies by Ciccone et al.(2013) and Stahmeyer et al.(2019) used to provide probabilities of recurrent stroke.. —: No reason to upgrade, ↑: reason to upgrade.[35; 37]

Author	Ciccone et al.(2013)
Risk of bias	Low risk.
Random sequence generation (selection bias)	*Low risk. "The study protocol provided for centralized, simple randomization online."*
Allocation concealment (selection bias)	*Unclear*
Blinding of participants and personnel (performance bias)	*High risk. Not possible to blind participants and treating personnel due to type of treatment.*
Blinding of outcome assessment (detection bias)	*Low risk. "Long-term clinical condition was assessed 90 days after randomization by means of a telephone interview by a single neurologist, who was not aware of treatment assignments."*
Incomplete outcome data (attrition bias)	*Low risk. "Intention-to-treat analyses were used throughout the study."*
Selective reporting (reporting bias)	*Low risk. Authors report outcomes of all patients - including patients receiving wrong treatment based on randomization.*
Inconsistency	Multiple 95% CIs include 1 and are not statistically significant ($\alpha = 0.05$). The study is downgraded.
Indirectness	The study does not differentiate between patients receiving tPA (70%) and those not receiving tPA (30%). The study is downgraded.
Imprecision	362 patients enrolled between 2008-2012
GRADE	Low

Table D.5: Detailed description of GRADE for Ciccone et al.(2013)[35].

Author	Stahmeyer et al.(2019)
Risk of bias	Low risk. The study is upgraded.
Failure to develop and apply appropriate eligibility criteria	*Unclear*
Flawed measurement of both exposure and outcome	*Low risk. Make own well-based assumptions and use all relevant ICD-codes.*
Failure to adequately control confounding	*Low risk. Make different subgroup analyses.*
Incomplete or inadequately short follow up	*Low risk. Make follow-up at both 3 months, 1 year, and 5 years.*
Inconsistency	All p-values except 1 are statistically significant ($\alpha = 0.05$). The results are reported in HR.
Indirectness	The study investigates German registry data. Germany has a Bismarck insurance system, and the study investigates one of the large insurance companies' data. The population is transferable to a Danish setting. The study includes all types of stroke - both ischemic and hemorrhagic. This current project investigates only ischemic stroke. Due to this, the study is not upgraded.
Imprecision	Large study population of 2145 patients. The study is upgraded.
GRADE	Moderate

Table D.6: Detailed description of GRADE for Stahmeyer et al.(2019)[37].

D.4 Slot et al.(2009) - mortality

Author	Risk of bias	Inconsistency	Indirectness	Imprecision	GRADE
Slot et al.(2009)	—	—	↑	↑	Low

Table D.7: Rate of trial by Slot et al.(2009) used to provide information about risk of dying in each mRS-state[38]. —: No reason to upgrade, ↑: reason to upgrade.

Author	Slot et al. (2009)
Risk of bias	High. The study is not upgraded.
Failure to develop and apply appropriate eligibility criteria	*Unclear*
Flawed measurement of both exposure and outcome	*High. In 1/3 registries included in Slot et al, functional state was assessed using "2 simple questions" and not the mRS-scoring system. In the remaining 2 registries, mRS was measured correctly.*
Failure to adequately control confounding	*Unclear*
Incomplete or inadequately short follow up	*Low risk. 6 and 12 month follow-up*
Inconsistency	Many overlapping CIs when RR is reported. The study is not upgraded.
Indirectness	The primary aim is not useful for our project, however the secondary aims are. The population and intervention are transferable. The study is upgraded one level.
Imprecision	The study includes a large population and the results are deemed trustworthy.
GRADE	Low

Table D.8: Detailed description of GRADE for Slot et al. (2009)[38].

Appendix E

Mortality - dataset

	mRS0-1	mRS2	mRS3	mRS4	mRS5
Cycle	1	1,12	1,66	1,92	2,57
0	0,01139	0,01276	0,01891	0,02188	0,02928
1	0,01139	0,01276	0,01891	0,02188	0,02928
2	0,01139	0,01276	0,01891	0,02188	0,02928
3	0,01139	0,01276	0,01891	0,02188	0,02928
4	0,01284	0,01438	0,02131	0,02465	0,03300
5	0,01284	0,01438	0,02131	0,02465	0,03300
6	0,01284	0,01438	0,02131	0,02465	0,03300
7	0,01284	0,01438	0,02131	0,02465	0,03300
8	0,01374	0,01539	0,02282	0,02639	0,03532
9	0,01374	0,01539	0,02282	0,02639	0,03532
10	0,01374	0,01539	0,02282	0,02639	0,03532
11	0,01374	0,01539	0,02282	0,02639	0,03532
12	0,01483	0,01661	0,02461	0,02847	0,03811
13	0,01483	0,01661	0,02461	0,02847	0,03811
14	0,01483	0,01661	0,02461	0,02847	0,03811
15	0,01483	0,01661	0,02461	0,02847	0,03811
16	0,01577	0,01766	0,02618	0,03028	0,04053
17	0,01577	0,01766	0,02618	0,03028	0,04053
18	0,01577	0,01766	0,02618	0,03028	0,04053
19	0,01577	0,01766	0,02618	0,03028	0,04053
20	0,01715	0,01921	0,02847	0,03293	0,04408
21	0,01715	0,01921	0,02847	0,03293	0,04408
22	0,01715	0,01921	0,02847	0,03293	0,04408
23	0,01715	0,01921	0,02847	0,03293	0,04408
24	0,01786	0,02001	0,02965	0,03430	0,04591
25	0,01786	0,02001	0,02965	0,03430	0,04591
26	0,01786	0,02001	0,02965	0,03430	0,04591
27	0,01786	0,02001	0,02965	0,03430	0,04591
28	0,02000	0,02239	0,03319	0,03839	0,05139
29	0,02000	0,02239	0,03319	0,03839	0,05139
30	0,02000	0,02239	0,03319	0,03839	0,05139
31	0,02000	0,02239	0,03319	0,03839	0,05139
32	0,02322	0,02600	0,03854	0,04457	0,05966
33	0,02322	0,02600	0,03854	0,04457	0,05966
34	0,02322	0,02600	0,03854	0,04457	0,05966
35	0,02322	0,02600	0,03854	0,04457	0,05966
36	0,02521	0,02823	0,04184	0,04840	0,06478
37	0,02521	0,02823	0,04184	0,04840	0,06478
38	0,02521	0,02823	0,04184	0,04840	0,06478
39	0,02521	0,02823	0,04184	0,04840	0,06478
40	0,02814	0,03151	0,04670	0,05402	0,07231
41	0,02814	0,03151	0,04670	0,05402	0,07231
42	0,02814	0,03151	0,04670	0,05402	0,07231
43	0,02814	0,03151	0,04670	0,05402	0,07231
44	0,03029	0,03393	0,05029	0,05816	0,07785
45	0,03029	0,03393	0,05029	0,05816	0,07785
46	0,03029	0,03393	0,05029	0,05816	0,07785
47	0,03029	0,03393	0,05029	0,05816	0,07785
48	0,03445	0,03858	0,05719	0,06614	0,08853
49	0,03445	0,03858	0,05719	0,06614	0,08853

	mRS0-2	mRS3-5
Cycle	1,12	2,57
0	0,01276	0,02928
1	0,01276	0,02928
2	0,01276	0,02928
3	0,01276	0,02928
4	0,01438	0,03300
5	0,01438	0,03300
6	0,01438	0,03300
7	0,01438	0,03300
8	0,01539	0,03532
9	0,01539	0,03532
10	0,01539	0,03532
11	0,01539	0,03532
12	0,01661	0,03811
13	0,01661	0,03811
14	0,01661	0,03811
15	0,01661	0,03811
16	0,01766	0,04053
17	0,01766	0,04053
18	0,01766	0,04053
19	0,01766	0,04053
20	0,01921	0,04408
21	0,01921	0,04408
22	0,01921	0,04408
23	0,01921	0,04408
24	0,02001	0,04591
25	0,02001	0,04591
26	0,02001	0,04591
27	0,02001	0,04591
28	0,02239	0,05139
29	0,02239	0,05139
30	0,02239	0,05139
31	0,02239	0,05139
32	0,02600	0,05966
33	0,02600	0,05966
34	0,02600	0,05966
35	0,02600	0,05966
36	0,02823	0,06478
37	0,02823	0,06478
38	0,02823	0,06478
39	0,02823	0,06478
40	0,03151	0,07231
41	0,03151	0,07231
42	0,03151	0,07231
43	0,03151	0,07231
44	0,03393	0,07785
45	0,03393	0,07785
46	0,03393	0,07785
47	0,03393	0,07785
48	0,03858	0,08853
49	0,03858	0,08853

50	0,03445	0,03858	0,05719	0,06614	0,08853	50	0,03858	0,08853
51	0,03445	0,03858	0,05719	0,06614	0,08853	51	0,03858	0,08853
52	0,03795	0,04250	0,06300	0,07286	0,09753	52	0,04250	0,09753
53	0,03795	0,04250	0,06300	0,07286	0,09753	53	0,04250	0,09753
54	0,03795	0,04250	0,06300	0,07286	0,09753	54	0,04250	0,09753
55	0,03795	0,04250	0,06300	0,07286	0,09753	55	0,04250	0,09753
56	0,04134	0,04630	0,06863	0,07938	0,10625	56	0,04630	0,10625
57	0,04134	0,04630	0,06863	0,07938	0,10625	57	0,04630	0,10625
58	0,04134	0,04630	0,06863	0,07938	0,10625	58	0,04630	0,10625
59	0,04134	0,04630	0,06863	0,07938	0,10625	59	0,04630	0,10625
60	0,04649	0,05207	0,07717	0,08925	0,11947	60	0,05207	0,11947
61	0,04649	0,05207	0,07717	0,08925	0,11947	61	0,05207	0,11947
62	0,04649	0,05207	0,07717	0,08925	0,11947	62	0,05207	0,11947
63	0,04649	0,05207	0,07717	0,08925	0,11947	63	0,05207	0,11947
64	0,05351	0,05993	0,08882	0,10273	0,13751	64	0,05993	0,13751
65	0,05351	0,05993	0,08882	0,10273	0,13751	65	0,05993	0,13751
66	0,05351	0,05993	0,08882	0,10273	0,13751	66	0,05993	0,13751
67	0,05351	0,05993	0,08882	0,10273	0,13751	67	0,05993	0,13751
68	0,06012	0,06734	0,09980	0,11543	0,15451	68	0,06734	0,15451
69	0,06012	0,06734	0,09980	0,11543	0,15451	69	0,06734	0,15451
70	0,06012	0,06734	0,09980	0,11543	0,15451	70	0,06734	0,15451
71	0,06012	0,06734	0,09980	0,11543	0,15451	71	0,06734	0,15451
72	0,06946	0,07780	0,11531	0,13337	0,17852	72	0,07780	0,17852
73	0,06946	0,07780	0,11531	0,13337	0,17852	73	0,07780	0,17852
74	0,06946	0,07780	0,11531	0,13337	0,17852	74	0,07780	0,17852
75	0,06946	0,07780	0,11531	0,13337	0,17852	75	0,07780	0,17852
76	0,07654	0,08572	0,12705	0,14695	0,19670	76	0,08572	0,19670
77	0,07654	0,08572	0,12705	0,14695	0,19670	77	0,08572	0,19670
78	0,07654	0,08572	0,12705	0,14695	0,19670	78	0,08572	0,19670
79	0,07654	0,08572	0,12705	0,14695	0,19670	79	0,08572	0,19670
80	0,08510	0,09531	0,14126	0,16338	0,21869	80	0,09531	0,21869
81	0,08510	0,09531	0,14126	0,16338	0,21869	81	0,09531	0,21869
82	0,08510	0,09531	0,14126	0,16338	0,21869	82	0,09531	0,21869
83	0,08510	0,09531	0,14126	0,16338	0,21869	83	0,09531	0,21869
84	0,10097	0,11308	0,16760	0,19386	0,25948	84	0,11308	0,25948
85	0,10097	0,11308	0,16760	0,19386	0,25948	85	0,11308	0,25948
86	0,10097	0,11308	0,16760	0,19386	0,25948	86	0,11308	0,25948
87	0,10097	0,11308	0,16760	0,19386	0,25948	87	0,11308	0,25948
88	0,11543	0,12929	0,19162	0,22163	0,29667	88	0,12929	0,29667
89	0,11543	0,12929	0,19162	0,22163	0,29667	89	0,12929	0,29667
90	0,11543	0,12929	0,19162	0,22163	0,29667	90	0,12929	0,29667
91	0,11543	0,12929	0,19162	0,22163	0,29667	91	0,12929	0,29667
92	0,12943	0,14496	0,21485	0,24851	0,33263	92	0,14496	0,33263
93	0,12943	0,14496	0,21485	0,24851	0,33263	93	0,14496	0,33263
94	0,12943	0,14496	0,21485	0,24851	0,33263	94	0,14496	0,33263
95	0,12943	0,14496	0,21485	0,24851	0,33263	95	0,14496	0,33263
96	0,14487	0,16226	0,24049	0,27815	0,37232	96	0,16226	0,37232
97	0,14487	0,16226	0,24049	0,27815	0,37232	97	0,16226	0,37232
98	0,14487	0,16226	0,24049	0,27815	0,37232	98	0,16226	0,37232
99	0,14487	0,16226	0,24049	0,27815	0,37232	99	0,16226	0,37232
100	0,16144	0,18082	0,26800	0,30997	0,41491	100	0,18082	0,41491
101	0,16144	0,18082	0,26800	0,30997	0,41491	101	0,18082	0,41491

102	0,16144	0,18082	0,26800	0,30997	0,41491	102	0,18082	0,41491
103	0,16144	0,18082	0,26800	0,30997	0,41491	103	0,18082	0,41491
104	0,17186	0,19248	0,28529	0,32997	0,44168	104	0,19248	0,44168
105	0,17186	0,19248	0,28529	0,32997	0,44168	105	0,19248	0,44168
106	0,17186	0,19248	0,28529	0,32997	0,44168	106	0,19248	0,44168
107	0,17186	0,19248	0,28529	0,32997	0,44168	107	0,19248	0,44168
108	0,18898	0,21166	0,31371	0,36284	0,48568	108	0,21166	0,48568
109	0,18898	0,21166	0,31371	0,36284	0,48568	109	0,21166	0,48568
110	0,18898	0,21166	0,31371	0,36284	0,48568	110	0,21166	0,48568
111	0,18898	0,21166	0,31371	0,36284	0,48568	111	0,21166	0,48568
112	0,21379	0,23944	0,35489	0,41048	0,54944	112	0,23944	0,54944
113	0,21379	0,23944	0,35489	0,41048	0,54944	113	0,23944	0,54944
114	0,21379	0,23944	0,35489	0,41048	0,54944	114	0,23944	0,54944
115	0,21379	0,23944	0,35489	0,41048	0,54944	115	0,23944	0,54944
116	0,24904	0,27893	0,41341	0,47816	0,64004	116	0,27893	0,64004
117	0,24904	0,27893	0,41341	0,47816	0,64004	117	0,27893	0,64004
118	0,24904	0,27893	0,41341	0,47816	0,64004	118	0,27893	0,64004
119	0,24904	0,27893	0,41341	0,47816	0,64004	119	0,27893	0,64004
120	0,27611	0,30925	0,45835	0,53013	0,70961	120	0,30925	0,70961

Appendix F

Full list of assumptions

Assumption	Reason/source
Target population:	
The model runs first cycle when patients are 65 years old.	[11]
All patients are dead at the age of 95.	Limitation of 120 cycles in TreeAge Pro.
Data from [11] are for all cases of stroke – both ischemic and hemorrhagic – but are assumed to be valid for AIS.	Ischemic strokes make up 85% of all stroke cases.
Alternatives:	
100% of patients suffering AIS in the 'current treatment'branch receives treatment.	[17; 40]
0% of patients suffering AIS in the 'no treatment' branch receive treatment.	Necessary assumption in order to make a correct comparison of the two alternatives.
Structure of Markov model:	
Patients can only move one mRS-state up or down per cycle. Not possible to move from e.g. mRS2 to mRS4	Simplification.
Patients will not change mRS-states between cycles	[40]
mRS-states are divided into three groups in 'no treatment strategy' mRS0-2: Good functional outcome mRS3-5: Poor functional outcome mRS6/death	Simplification.
Time horizon:	
Time horizon is 30 years/120 cycles.	Limitation of 120 cycles in TreeAge Pro.
Discount rate:	
4% per year, 0.985% per cycle.	[40]

Estimating initial probabilities for 'current treatment' branch:	
Probabilities for mRS at three months (cycle 0) are assumed to also be valid for six months (cycle 1).	[12; 23; 40; 58; 62]
Probabilities for mRS at cycle 2 are constant until cycle 120. No patients change mRS-state after cycle 2.	[12]
Estimating transition probabilities for 'current treatment' branch:	
Risk of recurrence at 1,2,3,4 and 5 years are constant. Risk of recurrence at e.g. one year is applied to all cycles corresponding to year 1 (cycle 4-7).	Simplification and lack of more detailed data.
Risk of recurrence is the same for all treatment types at 1,2,3,4 and 5 years.	Simplification and lack of more detailed data.
Risk of recurrence does not depend on mRS-state.	[40]
Patients cannot remit after suffering recurrence of AIS.	[40]
Patients can only get one recurrence of AIS per cycle.	Simplification.
Patients suffering recurrence of AIS have the probability of getting the four types of treatment as patients suffering initial AIS.	Simplification.
Article by Ciccone et al.(2013): 70% of all patients receive tPA. We assume, that 100% of patients are treated with tPA.	Simplification and no sub-group analyses in original article.
Mortality after recurrent stroke is the same as mortality after initial AIS.	Simplification.
Probability of staying in an mRS-state after AIS is 1.	[40]
Probability of remission and progression after AIS is 0.	[40]
Mortality after initial AIS is from three months but is applied to all cycles and assumed to be constant.	Simplification.
Mortality after AIS in mRS0-1 is the same as the background population.	[38]

Estimating utility values for 'no treatment strategy' branch	
Utility values are the same as the worst mRS-state in each group.	It is assumed that patient's utility value is worse when they do not receive any treatment.
Estimating transition probabilities for 'no treatment strategy' branch:	
Probabilities of ending up in different groups are: mRS0-2: 40% mRS3-5: 30% mRS6: 30%	[40]
Mortality is taken from the worst mRS-state in each group.	It is assumed that the risk of dying is higher when patients do not receive any treatment.
Costs:	
Costs for rehabilitation and physio-/ ergotherapist is applied to an mRS-state.	Based on symptoms [50]
Home care: mRS2 receives two visits per week. mRS3 receives five visits per week. mRS4 receives 10 visits per week.	Based on symptoms [50]
mRS5 is admitted to nursing home after discharge from hospital.	[50]
100% of patients take prophylactic clopidogrel after AIS.	According to RADS guidelines, Clopidogrel is first-line treatment for prophylaxis. Second- and third-line are not taken into consideration due to simplification [20]
100% of patients go to a routine check at their general practitioner within three months after starting prophylactic treatment with Clopidogrel.	[40]

Table F.1: List of all assumptions made. AIS: Acute ischemic stroke, mRS: Modified Rankin scale.

Appendix G

Markov model - Full tree

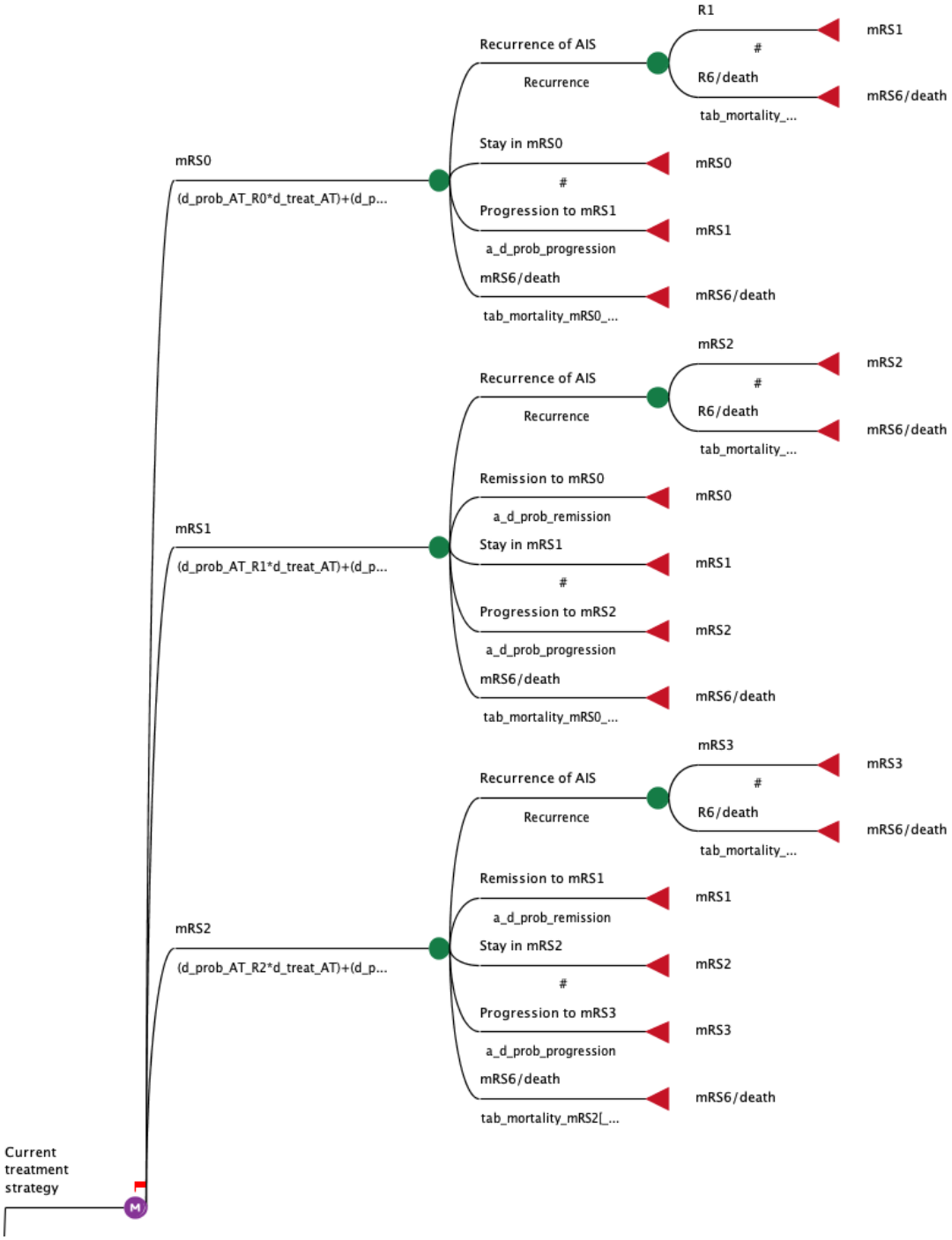


Figure G.1: The upper part of the 'current treatment strategy' branch.

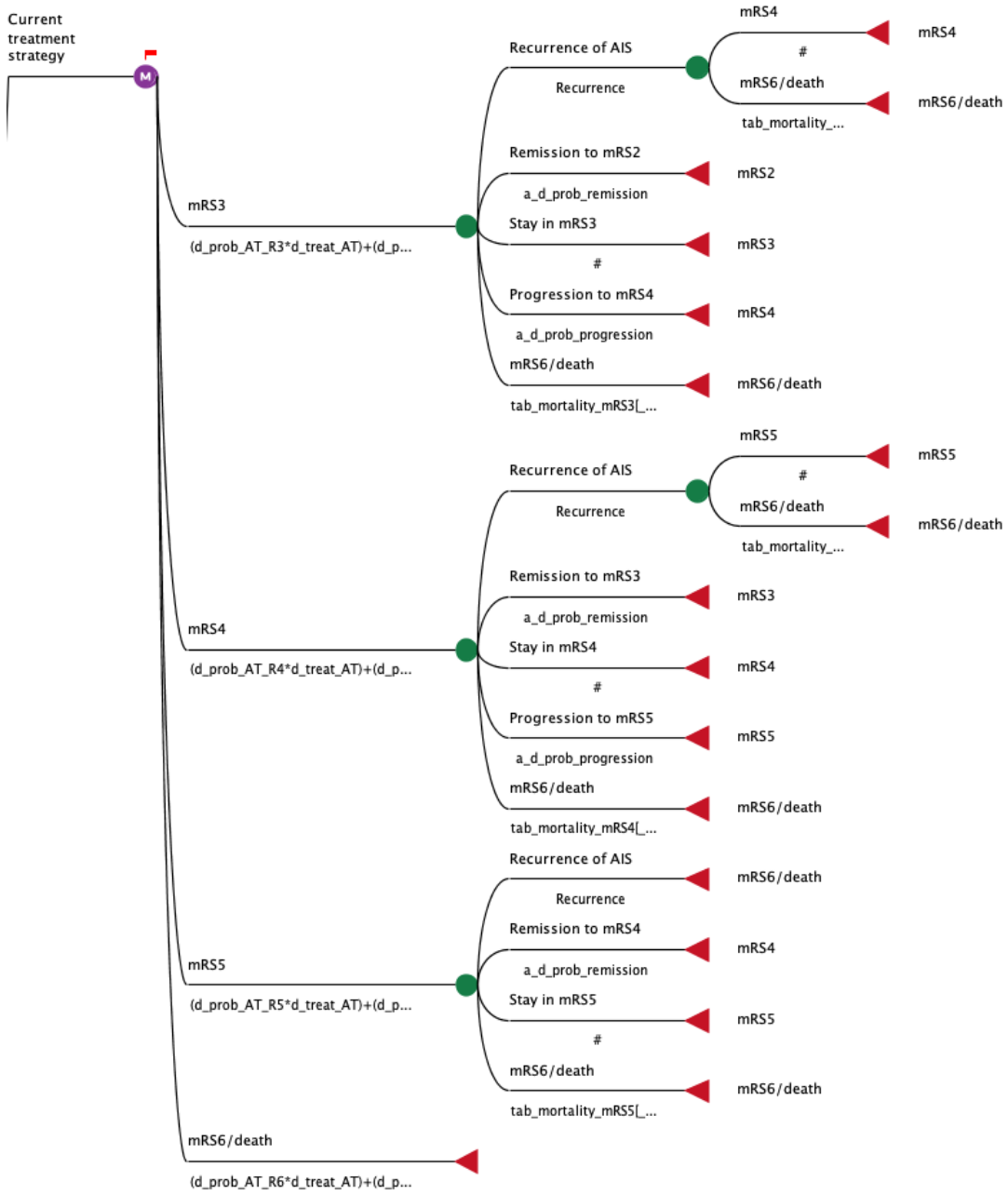


Figure G.2: The lower part of the 'current treatment strategy' branch.

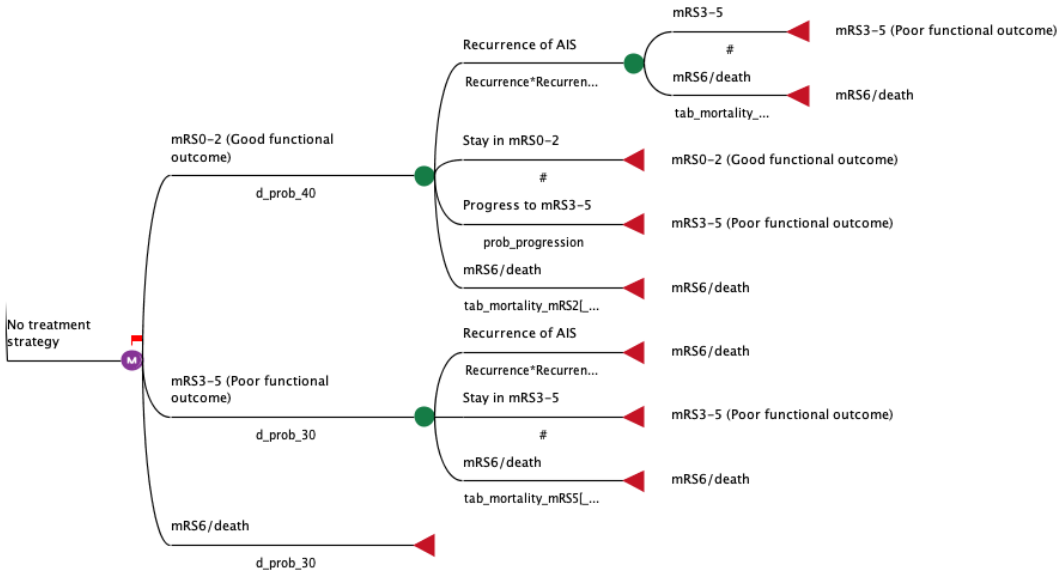
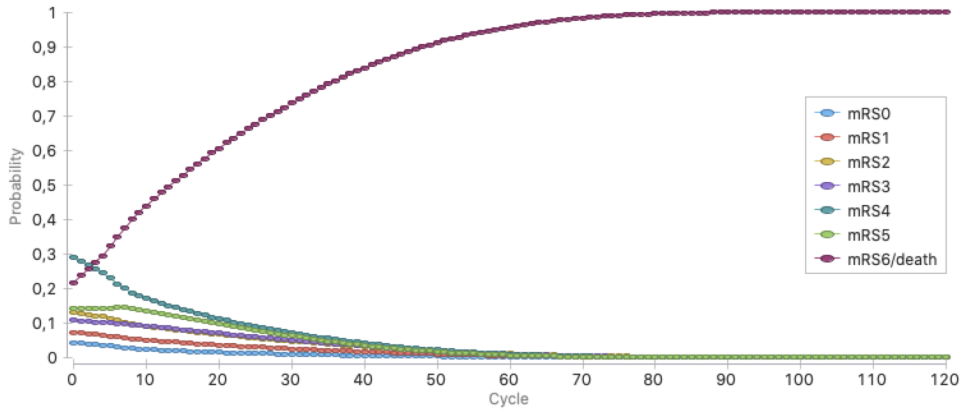


Figure G.3: The 'No treatment strategy' branch.

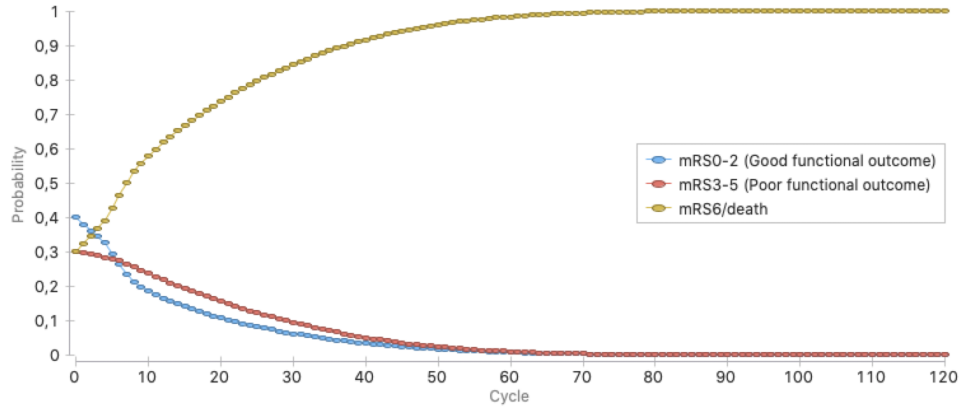
Appendix H

Distribution of health states in Markov model

Results from the Markov model show, that patients die rather quickly. Figure H.1 shows the probability of each health state for all 120 cycles.



(a) Current treatment strategy.



(b) No treatment strategy.

Figure H.1: Probabilities of the different health states as a function of cycles in the Markov model.

Approximately 100% of patients are dead in cycle 80 in the 'current treatment strategy' and in cycle 72 in 'no treatment strategy. This is shown in figure H.1.

Appendix I

Tornado analysis - full analysis

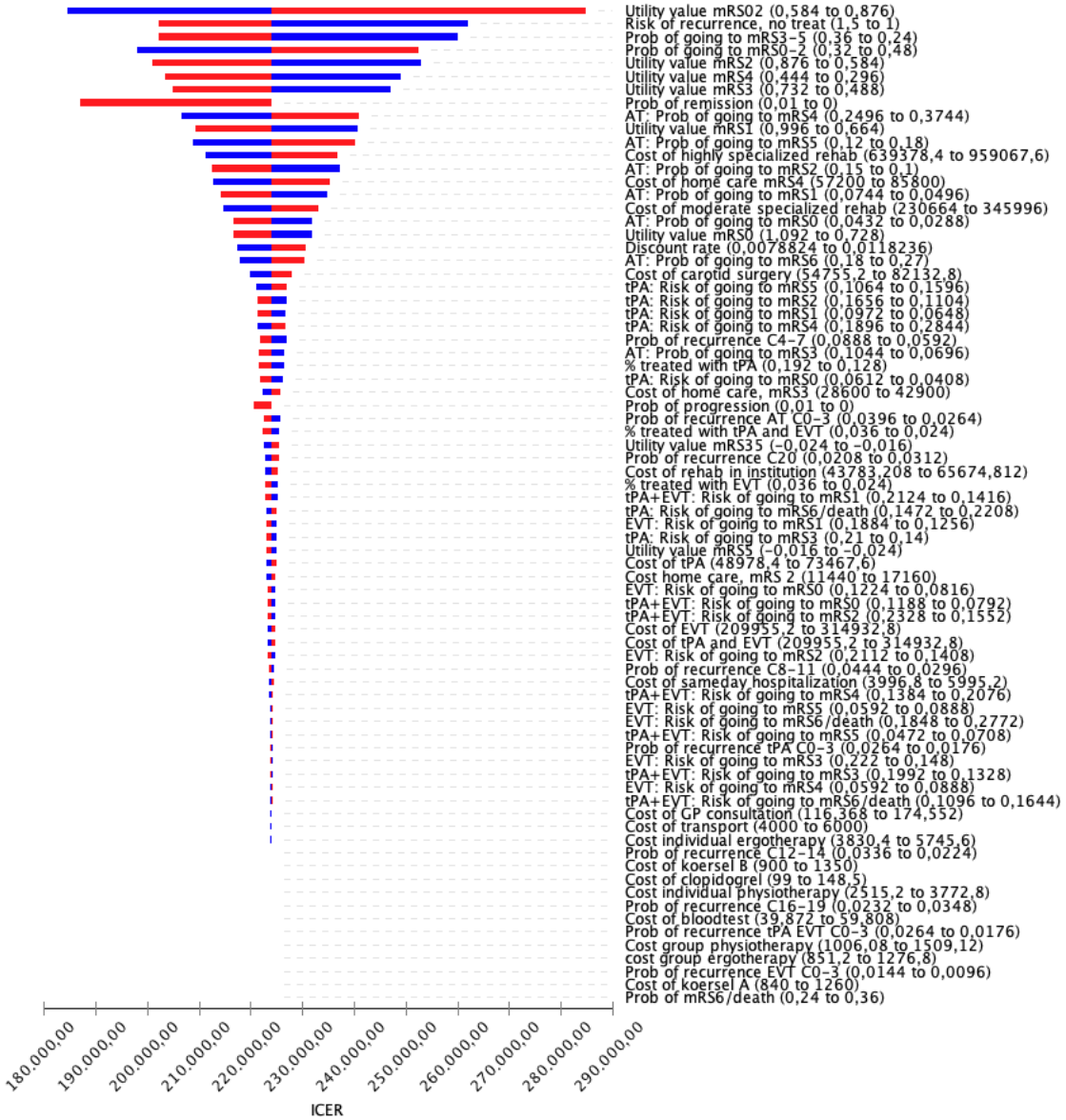


Figure I.1: Full tornado analysis showing the impact of each parameter on the final result. ICER: Incremental cost-effectiveness ratio.