TANDVÅRDS- OCH
LÄKEMEDELSFÖRMÅNSVERKET

Health Technology Assessment

Cost-effectiveness analysis of thrombectomy for treatment of acute severe ischemic stroke

Project group:
Janie Thurman, Bjorn Södergård, Nathalie Eckard, Caroline Nilsson, and Sanna Hiort

Medical experts:

Mia von Euler, MD, PhD, Specialist in Neurology and Clinical Pharmacology and Director of Karolinska Institutet Stroke Research Network at Södersjukhuset, Stockholm, Sweden
Gunnar Andsberg, MD, Neurology and Rehabilitation Medicine, Neurology, Skåne University Hospital, Lund, Sweden

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Reference number: 01009/2015
Postal address: PO Box 22520, 104 22 Stockholm, Sweden
Visiting address: Fleminggatan 7, Stockholm
Phone: + 46 8 568 420 50
www.tlv.se

Preface

In April 2012, the Dental and Pharmaceutical Benefits Agency (TLV) was commissioned by the Swedish Government to undertake economic evaluations of medical devices. Operations were conducted in the form of a trial commission and the final report was presented on 5 November 2013. The final report consisted partly of a health technology assessment (HTA) in the form of an economic evaluation of selected medical devices and partly an evaluation of how permanent operations could be designed. The commission was extended and during 2014, TLV drafted two HTA's. Its final report was submitted on 31 December 2014.

TLV was granted a continued commission for 2015 by the Swedish Government for performing economic evaluations of medical devices. A commission report will be submitted to the government by 31 December, 2015.
There are no Swedish recommendations regarding the use of thrombectomy. The National Board of Health and Welfare is currently in the process of revising the national guidelines for stroke care, which includes inquiries concerning the use of thrombectomy. TLV and the National Board of Health and Welfare have therefore collaborated regarding a literature review of medical evidence that form the foundation of TLV's economic evaluation.

This HTA aims to support healthcare equity and contribute to coordination at a national level by providing county councils access to the same basis for decision-making regarding the introduction of new healthcare methods. Within the framework of the commission, TLV does not make decisions but instead prepares HTA's to be used as a basis for decisions by the county councils.

Stockholm, 29 October 2015

Sofia Wallström
Director General

Content

Summary

TLV has been commissioned by the Swedish Government to make economic evaluations of medical devices. A commission report will submitted to the government by 31December 2015.

Sweden registered 23,600 healthcare cases of acute stroke in 2014. Stroke is the third most common cause of death and the leading cause of permanent physical impairment in adults. Stroke therefore affects patients' quality of life. The annual societal costs of stroke are estimated to be approximately 16 billion SEK annually.

Many stroke patients are treated with intravenous thrombolysis, an established and effective treatment. Interest in alternative therapies has increased in recent years, partly due to intravenous thrombolysis' limited efficacy for acute severe ischemic stroke, and partly because some patients have contraindications to the treatment. In additional to standard treatment with intravenous thrombolysis (if indicated), thrombectomy is now an alternative treatment option for acute severe ischemic stroke. Thrombectomy involves inserting a catheter and stent retriever into an artery in the groin and pulling out the blood clot from the brain.

TLV and the National Board of Health and Welfare have collaborated regarding literature review of medical evidence that forms the foundation of the cost-effectiveness analysis. This medical evidence is based on five published clinical studies: MR CLEAN, ESCAPE, EXTEND IA, SWIFT PRIME and REVASCAT. The studies had a greater clinical efficacy and increased patient benefit in patients treated with intravenous thrombolysis in combination with thrombectomy compared to patients treated only with intravenous thrombolysis. Thrombectomy is now recommended internationally as treatment when intravenous thrombolysis is deemed inadequate.

In Sweden, there are not yet any national treatment recommendations for thrombectomy. The purpose of the HTA is to support healthcare equity and contribute to national coordination by providing county councils access to the same basis for decisions regarding the introduction of new methods in healthcare. The HTA is based on the best available knowledge. Within the framework of the commission, TLV does not make decisions but instead produces economic evaluations for decisions taken by the county councils.

The result of TLV's cost-effectiveness analysis indicates that thrombectomy is very likely a cost-effective treatment for acute severe ischemic stroke. In TLV's base-case scenario, the cost per QALY gained is low. The proportion of stroke patients suitable for thrombectomy and in need of special accommodation is uncertain. Therefore, a sensitivity analysis was made to

calculate an extreme case where seriously ill patients have significantly higher health and social care costs in comparison with the general stroke population. The results of the sensitivity analysis showed that health and social care costs had a major impact on the result and indicate that the result should be cost saving. TLV has assumed that there is the same willingness to pay for medical devices as for pharmaceuticals within the pricing and reimbursement system. TLV cannot, however, say if this is consistent with the county councils' actual willingness to pay.

TLV's HTA's normally consist of two parts. The first part describes the state of knowledge regarding the current situation, treatment practices and an economic evaluation. The second part describes the organisational changes that the introduction of a new method may require, such as, education and training, budget, and needs for evaluation and follow-up.

The second part of the HTA for thrombectomy will be published separately. This has been done to meet the county councils' needs for early delivery of the first part, which includes the economic evaluation. In the second part, TLV will follow-up this evaluation by investigating aspects associated with organisational consequences and budget impact within healthcare, as well as relevant ethical issues. The second part of the HTA will be published before the summer of 2016.

1 TLV:s medical device commission

1.1 The government commission

In April 2012, TLV was commissioned by the Swedish Government to conduct economic evaluations of medical devices in the form of a trial commission. The final report was submitted in November 2013.

In connection with TLV's final report, the government expanded the trial commission. The new trial commission included further developing how TLV should evaluate medical devices and to make economic evaluations of at least two new medical device methods. The government later extended the trial commission for TLV to make further economic evaluations of medical device methods for 2015. A commission report will be submitted to the government by December 31, 2015.

According to the government, the following product aspects should be considered when selecting methods to be assessed:

- Target a large patient population
- Capable of creating increased patient involvement and autonomy
- Have a cost-saving potential in healthcare, especially in primary care and specialised outpatient care

The economic evaluations should, among other aspects, aim to support healthcare providers with procurements and decisions regarding the introduction of new medical device methods. In order for the HTA's to be most effective, they should be performed in the early stages of the product life cycle of a medical device, sometimes even before published clinical data are available, but after CE-marking.

1.2 The foundation for TLV's work

1.2.1 The ethical platform

TLV's HTA's are based on the ethical platform and aim to achieve as much health as possible for tax funds spent in the healthcare sector. The ethical platform used by the healthcare sector, was decided upon by the Swedish parliament, and is used when setting priorities within publicly funded healthcare. The ethical platform is based on three principles: the human dignity principle, the needs and solidarity principle, and the cost-effectiveness principle.

The principle of human dignity is an overriding principle that means that everyone has an equal value and same rights to healthcare. The principle can be said to constitute the framework within which prioritisation decisions

must always be made. The needs and solidarity principle means that if prioritisation must be made between measures, most healthcare resources should be given to those with the greatest needs, such as patients with the most severe conditions and patients with the lowest quality of life. The cost-effectiveness principle means that when choosing between different measures, a reasonable relationship should exist between cost and effect measured in improved health and quality of life. In deciding on priorities, a balance therefore needs to be reached between the needs and solidarity principle and the cost principle.

In summary, the cost-effectiveness principle is related to the amount of benefit for patients created per Swedish krona (SEK), while the needs and solidarity principle is about the amount of benefit created for patients that should be distributed fairly. TLV balances these principals by accepting less health benefits per SEK the more severe an illness is.

1.2.2 Societal perspective

An important basis in TLV's economic evaluations of medical devices is the societal perspective. A societal perspective means that costs outside of healthcare are also included in the economic evaluation. Costs outside of healthcare can be called indirect costs. This distinguishes TLV's work from that which the county councils usually carry out. Not all indirect costs are, however, taken into account in this HTA. Costs incurred during care for dependents by closely related care givers have not been included.

1.2.3 Economic evaluations sometimes have limited evidence

Prior to a county council's decision on introducing a new treatment, purchasing, or procurement of a new treatment, it is essential to conduct an economic evaluation. The more evidence there is about a medical device, the less the uncertainty there will be in the evaluation of its cost effectiveness. Economic models are always associated with some uncertainty. The evidence can be flawed and validated data might not be available. Despite this, TLV has determined that it is important to provide HTA's based on best available data, even if some uncertainty exists, rather than no decision support at all. Lack of evidence always requires that the HTA takes into account the specific problems and difficulties that are characteristic for medical devices in their early stages.

1.2.4 The evidence base regarding thrombectomy is well established

This HTA is primarily based on five randomised controlled trials; MR CLEAN [1], ESCAPE [2], EXTEND IA [3], SWIFT PRIME [4] and REVASCAT [5], all of which are published. TLV deems the availability of evidence to be good.

1.2.5 The health technology assessment

The purpose of the HTA is to support healthcare equity and contribute to national coordination by providing county councils access to the same basis for decisions concerning the introduction of new healthcare methods. The HTA is derived from the best available knowledge. Its conclusions are not binding, but should be used as a guide for county councils.

In this HTA, TLV collaborated with the National Board for Health and Welfare and the Association of Local Authorities and Regions (SKL) Program Council for stroke that is assessing thrombectomy.

TLV's HTA's consists of two parts. The first part of the HTA describes the state of knowledge regarding the current situation, treatment practices and economic evaluation. The second part of the HTA describes the organisational changes that the introduction of a new method may require, such as education and training, budget, needs for evaluation and follow-up.

The two parts will be published separately in this case. The reason for doing this is to meet the county councils' needs for early delivery of the first part, which includes the economic evaluation of thrombectomy. In the second part, TLV will follow up this evaluation by investigating aspects associated with healthcare organisational consequences and budget impact, as well as relevant ethical issues. The second part of the HTA will be published before the summer of 2016.

2 Treatment of stroke by intravenous thrombolysis and thrombectomy

Summary

Stroke is a generic name for ischemic stroke (stroke caused by a blood clot) and a haemorrhagic stroke (cerebral haemorrhage). During an ischemic stroke, parts of the brain suffer oxygen deprivation due to a blood clot blocking blood flow in a vessel of the brain. This leads to a cerebral infarction if blood flow is not restored in time. In Sweden, 23,600 cases of acute stroke were registered in 2014. Stroke is the third most common cause of death and the leading cause of neurological impairment in adults.

Intravenous thrombolysis is an established and effective treatment if initiated within 4.5 hours from the onset of stroke. However, this treatment is not always sufficient and cannot be used in patients with a high risk of bleeding.

If sudden occlusion of large arteries of the brain occurs, patients risk extensive brain damage. Intravenous thrombolysis is effective if a minor clot is located in a smaller artery. Although, the larger the clot, the less effective is the treatment to dissolve it. Until recently there has lacked an effective treatment for patients most likely to suffer the most extensive brain damage. However, there is now an additional treatment option for acute severe ischemic stroke, thrombectomy. This treatment involves inserting a catheter, and a stent retriever, into an artery in the groin and pulling out the blood clot from the brain.

There are currently no Swedish national recommendations for the use of thrombectomy. The National Board of Health and Welfare is in the process of updating the national guidelines for stroke care concerning the use of thrombectomy. TLV and the National Board of Health and Welfare have therefore collaborated regarding the literature review of medical evidence. Thrombectomy is recommended internationally as a treatment when intravenous thrombolysis is deemed inadequate.

2.1 Stroke

Stroke is a generic name for ischemic stroke (stroke caused by a clot) and haemorrhagic stroke (cerebral haemorrhage) where cardiovascular disease is an underlying cause. During an ischemic stroke, parts of the brain suffer oxygen deprivation due to a blood clot blocking the flow of blood in a vessel of the brain. This leads to a cerebral infarction if blood flow is not restored in time. The symptoms suffered by the patient during ischemic stroke vary and depend, among other things, on which area of the brain is affected and how extensive the brain damage is.

Sweden's national quality register for stroke (RiksStroke), registered approximately 23,600 cases of acute stroke in 2014 [6]. The registered cases include both first-time stroke and relapses. Compared with 2013, this is a reduction of approximately 800 cases [6]. The declining trend in recent years continues and is likely due to a reduced risk of developing cardiovascular disease [6]. Of the registered stroke cases in 2014, 86 percent were due to a clot [6, 7] and 13 percent were due to bleeding in the brain tissue [6]. Bleeding between the meninges (subarachnoid haemorrhage) affects approximately five percent of all adult stroke patients [7] but these cases are not registered in RiksStroke.

Approximately one in five patients who suffer a stroke dies. This makes stroke the third most common cause of death [8, 9]. Stroke is the leading cause of long-term physical impairment in adults, resulting in major health and social care needs [9], and usually reduces quality of life for patients.

Patients with ischemic stroke that have a blockage in the brain's large vessels in the anterior circulation belong to the group with the greatest risk of death or suffering severe physical impairment. Ischemic stroke in the basilar artery has an even poorer prognosis.

2.1.1 High societal costs for stroke

The average cost of treating an average stroke patient is around SEK 162,500 annually per patient the first year after the stroke. The average cost of health and social care as well as reduced ability to work for an average patient is estimated to total SEK 741,000 per individual and life time [10]. This means that the total societal costs of those patients who had a stroke in 2009 corresponded to approximately 16.1 billion SEK [10]. The group of patients with occlusion of large vessels in the brain's anterior circulation is likely to have an even higher cost per average patient.

2.2 Treatment of stroke

2.2.1 Intravenous thrombolysis is an effective treatment of stroke

Intravenous thrombolysis with alteplase (a clot dissolving pharmaceutical) has been an established treatment of cerebral infarction for a considerable time [11]. There is scientific evidence for its treatment effectiveness and safety [11].

Treatment with intravenous thrombolysis within 3 hours after the first symptoms significantly improves the chance of complete or nearly complete recovery. However, the positive clinical effect decreases over time [12]. This means that if treatment is initiated between 3 to 4.5 hours after onset of symptoms, the probability of complete or nearly complete recovery is still high, but is a drastic decrease compared with cases where treatment was initiated sooner [12]. The dissolution of blood clots after intravenous thrombolysis may take up to 2 hours [13].

The National Board of Health and Welfare national guidelines for stroke care from 2009 were updated in 2014 regarding the guidelines for intravenous thrombolysis [14]. According to these guidelines, thrombolysis should be offered to all patients, regardless of age, within 4 hours and 30 minutes of the first symptoms of stroke [14]. Regarding elderly patients (over 80 years), the risk of treatment should especially be weighed against the treatment benefits if the time from first symptoms exceeds 3 hours. [14].

2.2.2 Risks and side effects of intravenous thrombolysis

There are groups of patients with ischemic stroke who cannot be treated with intravenous thrombolysis, primarily due to a high risk of bleeding. The largest group consists of patients treated with anti-coagulants such as warfarin (INR> 1.7) or newer types of anti-coagulants (Pradaxa, ELIQUIS or Xarelto). Other groups are those who have recently undergone surgery, patients with very severe neurological symptoms, previous cerebral haemorrhages, and also cases of suspected subarachnoid haemorrhage despite normal CT scans.

Between five and six percent of patients experience intracranial haemorrhage with clinical deterioration after treatment with intravenous thrombolysis. This is a serious side effect caused by a ruptured vessel in the brain resulting in bleeding [6].

2.2.3 Intravenous thrombolysis is inadequate for acute severe ischemic stroke

When sudden occlusion of the brain's major arteries occurs, patients risk extensive brain damage. In the majority of patients with acute ischemic stroke, the smaller cerebral arteries are affected and result in more limited brain damage. Treatment with intravenous thrombolysis is effective on minor clots located in the small arteries. Consequently, there is an effective treatment for the majority of patients with acute ischemic stroke. The problem with intravenous thrombolysis is, however, that the larger the clot, the less effective is the treatment to dissolve it. If a clot is more than 8 mm long and blocks blood flow in the first section of the middle cerebral artery, treatment with intravenous thrombolysis is unable to restore blood flow [15]. Furthermore, blood flow is only restored in one in twenty patients after treatment with intravenous thrombolysis if the clot is located in the last section of the carotid artery, which is the main artery supplying the brain [16]. Until recently, there has been no effective treatment for patients who are most likely to suffer the most extensive brain damage.

2.2.4 Thrombectomy

Thrombectomy is another treatment option for acute severe ischemic stroke. This treatment involves inserting an instrument into the femoral artery that is guided up to a blood clot in the brain's vessel where the blood clot is mechanically removed. This intervention is therefore a more invasive treatment than thrombolysis, which is accomplished by an intravenous infusion of a pharmaceutical.

The techniques that have been used for thrombectomy have been developed over time. Previous generations of the technique have not proven to be sufficiently effective [17-20]. The breakthrough for mechanical thrombectomy came with the development of stent retrievers [4, 21].

Stent retrievers consist of a stent, a metal mesh cylinder that folds out and captures the blood clot. The clot becomes trapped in the metal mesh and can then be extracted from the vessel. The procedure may need repeating if the blood clot or part of it remains and continues to block the blood circulation [22, 23]. Subsequent references to thrombectomy in this HTA refer to this method.

In the spring of 2016, TLV will publish the second part of the HTA on thrombectomy that focuses on the organisational aspects. It should, however, already be noted here, that thrombectomy is a highly specialised intervention. Those who perform interventions with thrombectomy must be specialised in neuro-intervention and perform many of these interventions in order to maintain their skills. Most studies conducted have requirements on the number and frequency of performed thrombectomy interventions.

For the results of the studies to be reproduced, it is reasonable to require a similar level of experience. The intervention is carried out in only a few hospitals in Sweden. Moreover, relatively few patients in Sweden are treated with thrombectomy.

Only estimated numbers of expected trombektomi in a western population currently exist and these are based on the number of patients treated with intravenous thrombolysis. According to the estimate, approximately 20-30 percent of patients who meet the criteria for intravenous thrombolysis are eligible for thrombectomy therapy [24]. According to RiksStroke, 2271 patients were treated by intravenous thrombolysis in Sweden in 2014. Hospitals with well-functioning healthcare chains for intravenous thrombolysis treat more than 3000 patients with intravenous thrombolysis. Based on this number of intravenous thrombolysis treatments, the Swedish need for thrombectomy interventions is estimated to be between 450 and 900. Another way to estimate the number of thrombectomy interventions is to use data from the Karolinska University Hospital, which is the leading centre for thrombectomy in Sweden. In 2012, the proportion of thrombectomy interventions per 100,000 inhabitants was 5.3, corresponds to about 510 interventions annually [25]. The latter figure is consistent with a previous estimate of approximately 550 thrombectomies performed annually within 3-4 years [26].

The EVAS-register (EndoVascular treatment of Acute Stroke) is a national registry where detailed information regarding performance, results of various diagnostic methods, and the occurrence of complications of interventions are recorded [27]. The registry has published its first annual report [27] presenting data from treatments performed from July 1, 2013 to December 31, 2014. The registry is expected to prove valuable for monitoring effects of the treatment in patient groups. There is also an international research registry (SITS registry) at Karolinska Institutet where endovascular treatments for stroke are recorded.

There are currently no Swedish national recommendations for the use of thrombectomy. There are, however, records kept by the centres for thrombectomy in Sweden. The National Board of Health and Welfare is in the process of revising the national guidelines for stroke care, regarding the use of thrombectomy. TLV has therefore collaborated with the National Board of Health and Welfare concerning the medical part of the HTA.

2.2.5 Thrombectomy is recommended internationally

The first organisations to publish recommendations regarding thrombectomy were the European Stroke Organisation (ESO), European Society of Minimally Invasive Neurological Therapy (ESMINT) and the European Society of Neuroradiology (ESNR) that, in connection with the Karolinska Stroke Update Conference, published a consensus document

[28]. The recommendations were based on several consecutive studies which demonstrated a positive effect of thrombectomy: MR CLEAN [1] ESCAPE [2], EXTEND IA [3], SWIFT PRIME [4] and REVASCAT [5], 2015.

These organisations recommend, that thrombectomy be used in acute stroke patients with a blockage of a large artery in the anterior circulation up to six hours after the first symptoms in combination with intravenous thrombolysis performed within 4.5 hours. [28] If intravenous thrombolysis is not to be used, thrombectomy is recommended as the first-line treatment of ischemic stroke caused by a blockage in a major blood vessel [28].

The American Heart Association / American Stroke Association published recommendations in July 2015 [29]. According to the recommendations [29], patients who are eligible for intravenous thrombolysis should receive this treatment even if thrombectomy is considered. To be eligible for thrombectomy, patients must be over 18 years and have an obstruction of the last segment of the carotid artery (distal internal carotid artery) or middle cerebral artery first segment (proximal middle cerebral artery (M1)) [29]. Thrombectomy should be initiated within 6 hours and intravenous thrombolysis should have been applied within 4.5 hours [29].

Canadian Stroke Best Practice Recommendations, published in August 2015 [30], state that thrombectomy is recommended in Canada if the patient can be treated within six hours. Thrombectomy can be used if the patient has received intravenous thrombolysis or if the patient cannot be treated with intravenous thrombolysis. The consensus document that the European Stroke Organisation (ESO), European Society of Minimally Invasive Neurological Therapy (ESMINT) and the European Society of Neuroradiology (ESNR) published in connection with the Karolinska Stroke Update Conference [28] recommended stent retrievers approved by healthcare providers when thrombectomy was to be performed. They also noted that other thrombectomy instruments or instruments for proximal aspiration, also approved by healthcare providers, could be used if quick, complete and safe recanalization could be achieved.

The American Heart Association / American Stroke Association, [29] has recommended stent retrievers with the motivation that other products for thrombectomy have not been sufficiently evaluated and because the majority of patients (82 to 100 percent in the most recent studies [1-5]), have been treated with stent retrievers. Other thrombectomy instruments were used in some cases, representing 2 to 14 percent of cases. According to the recommendations [29], there is a lack of published randomised clinical trials demonstrating clinical efficacy for other thrombectomy products in comparison with stent retrievers.

2.2.6 Comparative treatment option

Thrombectomy is used as an additional treatment to intravenous thrombolysis or as a primary treatment if intravenous thrombolysis cannot be administered. The most relevant comparative treatment to thrombectomy as an additional treatment to intravenous thrombolysis, and the option which has the best safety data, is, treatment with intravenous thrombolysis alone. This is also the treatment compared to thrombectomy, the intervention treatment; see Chapter 4. The patients referred to in the remainder of this HTA are patients with acute severe ischemic stroke.

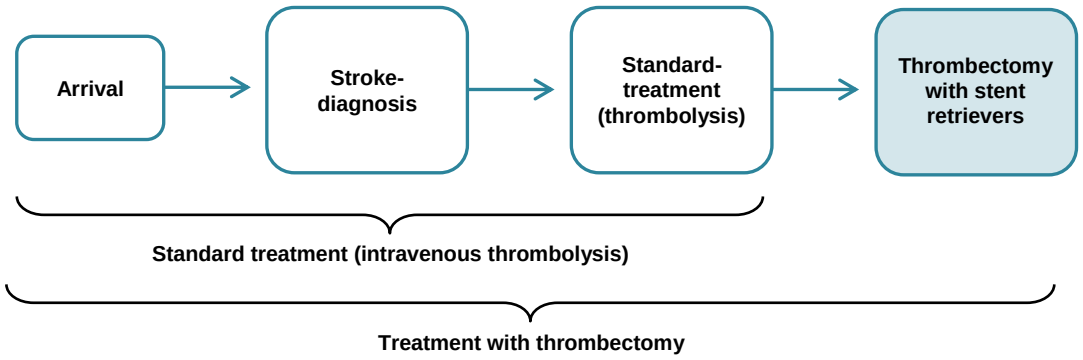

Figure 1. Overview of comparative treatment options

3 Clinical efficacy and patient benefit

Summary

This HTA compares two treatments for stroke:

1) Treating the patient with only intravenous thrombolysis
2) Treating the patient with intravenous thrombolysis and thrombectomy as an additional treatment

The HTA is based on five studies: MR CLEAN, ESCAPE, EXTEND IA, SWIFT PRIME and REVASCAT.

A summary of the five studies shows that three months after a stroke, a greater proportion of patients treated with thrombectomy had less physical impairment with the possibility to live independent lives without the need of assistance compared with patients who received no additional treatment.

Unless otherwise stated, this chapter is based on the literature review of medical evidence conducted by the Board of Health and Welfare.

3.1 Five studies have demonstrated the efficacy of stent retrievers

The HTA is based on five studies: MR CLEAN [1], ESCAPE [2], EXTEND IA [3], SWIFT PRIME [4] and REVASCAT [5][1]. As previously mentioned, there are older studies which examine the efficacy of thrombectomy. However, these studies were for older endovascular techniques. The results of these studies found no superior clinical efficacy when compared to thrombolysis. This is likely due to a combination of ineffective endovascular techniques and no requirement of proven obstruction suitable for endovascular treatment with computer angiographic scans to select and randomise patients.

The five studies are relatively similar in study design as they were all prospective, randomised and open-label treatment with blinded endpoint (PROBE).

[1] From these five studies, it appears that the stent retrievers primarily used are the Solitaire FR (Medtronic) and the Trevo ProVue (Stryker Neurovascular). This does not exclude that additional stent retrievers may also have been used.

3.1.1 mRS-scale measures physical impairment

Physical impairment is related to quality of life and subsequent treatment costs for patients who have suffered a stroke [31-33]. The scale central in the five studies [1-5] is the modified Rankin Scale (mRS-scale), which is a common tool for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke [31]. This scale is between zero and six, where zero corresponds to no residual disability and six equals death, see Table 1. The mRS scale is considered a global scale to estimate the patients' functional impairment following stroke [34].

Table 1. Description of physical impairment and functional independence according to the mRS scale

mRS-scale	Symptom description
mRS 0	No symptoms
mRS 1	No significant disability, despite symptoms; able to perform all usual duties and activities
mRS 2	Slight disability; unable to perform all pervious activities but able to look after own affairs without assistance
mRS 3	Moderate disability; requires some help, but able to walk without assistance
mRS 4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
mRS 5	Severe disability; bedridden, incontinent and requires constant nursing care and attention
mRS 6	Death

3.2 Patients studied in the five studies were relatively similar

Inclusion criteria for the five studies, such as a description of the factors that must be met for a patient to be eligible for inclusion in the five studies, were acute ischemic stroke with symptoms from the anterior circulation vessels. Detection of a blockage in any of the large vessels in the anterior circulation was mandatory.

The patients studied had relatively similar background data. Their average age was 65-70 years, and all had suffered a severe stroke, but had limited spreading of brain damage.

The majority of patients with acute ischemic stroke assessed in the five studies had occlusion of either the carotid artery last segment (26 percent) or the middle cerebral artery first segment (65 percent of the first segment and 7 percent of the second segment)[35]. Before treatment, the majority had pronounced neurological symptoms. Impairment caused by a stroke is measured with a clinical stroke scale called the NIH Stroke Scale (NIHSS). Clinical examination according to this scale estimates 15 different symptoms, such as paralysis of the arm or leg, loss of vision, language impairment and sensory loss (being unaware of stimuli to one side). According to the scale, patients without clinical symptoms score 0 points. Mild symptoms score up to 5 points, moderate between 6 and 12 points, and severe from 13 to 19 points. The most severe symptoms can result in scores just over 25 points. The average patient in the five studies had 17 points according to NIHSS, which differs significantly from the average stroke patient in Sweden who has around 3 points [6]. An average patient in the studies thus had pronounced paralysis of the arm and leg (hemiparesis), decreased vision or blindness in half the visual field (hemianopsia) and either great difficulty talking (dysphasia and dysarthria) or sensory loss. If the vascular obstruction was not successfully removed in time, these patients run an imminent risk of suffering extensive brain damage and have a high risk of severe neurological physical impairment or death [36, 37].

The majority of patients in both groups received intravenous thrombolysis; 68-100 percent in the intervention group and 78-100 percent in the control group.

All five trials showed good results. Four of the studies were discontinued; three due to preliminary results demonstrating overwhelmingly positive effects and, one due to ethical reasons since other studies demonstrated the positive effects of thrombectomy. This resulted in that a total of 1288 patients enrolled in the five studies instead of the planned 2623. The treatment results for patients who had already been included in the studies were published.

3.3 Thrombectomy has better clinical efficacy in acute severe ischemic stroke

The studies show that additional treatment with thrombectomy (with stent retrievers in the majority of cases) gives an absolute difference of 19.8 percentage mRS points compared with standard treatment, which in the majority of cases was intravenous thrombolysis. The results apply for functional independence three months after onset. In these studies, functional independence means that patients can cope without help and can live an independent life, a measurement of 0-2 on the mRS scale. The proportion of patients who could live with functional independence was thus

higher for those who received thrombectomy than for those who did not receive thrombectomy, see Table 2.

Increase or decrease in the mortality risk was not seen. The studies also failed to demonstrate an increased or decreased risk of symptomatic intracerebral haemorrhage, (bleeding inside the brain tissue), or intracranial haemorrhage, (cerebral haemorrhage with clinical worsening).

Complications considered to be related to thrombectomy were vessel dissection (damage leading to bleeding in the vascular wall) or vascular penetration (vessel punctured) with subsequent sub-arachnoid haemorrhaging (bleeding between the meninges), but this only occurred in a limited proportion of patients treated (0 to 3.7 percent and 0 to 4.1 percent). The MR CLEAN study showed an increased risk of acute ischemic stroke in another vascular territory. In the intervention group, the proportion was around 6 percent, and 0.5 percent in the control group. The ESCAPE study showed an increased risk for new stroke in the patients treated. In the intervention group, the proportion was around 5 percent with 2 percent in the control group.

3.3.1 Weighted results of the five studies

The results of all five studies have been weighted according to the number of patients in each study, see Table 2. The weighted results and the results from each individual study form the basis for the cost-effectiveness analysis as described in Chapter 4.

Table 2. Results of the studies, reported as weighted together and individually according to the mRS-scale

	mRS 0	mRS 1	mRS 2	mRS 3	mRS 4	mRS 5	mRS 6
All studies							
Thrombectomy	0,10	0,17	0,19	0,17	0,15	0,06	0,15
Standard treatment	0,05	0,08	0,14	0,16	0,25	0,14	0,19
MR CLEAN							
Thrombectomy	0,03	0,09	0,21	0,18	0,22	0,06	0,21
Standard treatment	0,00	0,06	0,13	0,16	0,30	0,12	0,22
ESCAPE							
Thrombectomy	0,15	0,21	0,18	0,16	0,13	0,07	0,10
Standard treatment	0,08	0,10	0,12	0,15	0,24	0,12	0,19
EXTEND-IA							
Thrombectomy	0,26	0,26	0,20	0,17	0,00	0,03	0,09
Standard treatment	0,17	0,11	0,11	0,11	0,17	0,11	0,20
SWIFT PRIME							
Thrombectomy	0,17	0,26	0,17	0,12	0,15	0,03	0,09
Standard treatment	0,09	0,11	0,16	0,17	0,22	0,13	0,13
REVASCAT							

Thrombectomy	0,07	0,17	0,19	0,18	0,08	0,12	0,18
Standard treatment	0,06	0,07	0,16	0,19	0,17	0,20	0,16

4 Cost-effectiveness analysis

Summary

The aim of the cost-effectiveness analysis was to quantify the effect on quality of life, life length and costs. The results are based on the clinical efficacy taken from five published clinical trials. These show that treatment with thrombectomy, as a supplement to intravenous thrombolysis, offers health benefits to patients with acute severe ischemic stroke.

The results of the cost-effectiveness analysis indicate that thrombectomy is highly likely a cost effective method of treatment. TLV's base-case scenario resulted in a low cost per QALY gained. The proportion of patients with a stroke eligible for thrombectomy and in need special living accommodation is uncertain. A sensitivity analysis was therefore made to account for a significantly higher health and social care costs compared with the general stroke population. The results of the sensitivity analysis showed that health and social care costs had a major impact on the result and indicate that the result should be cost saving.

4.1 Assumptions that affect economic evaluations

Economic evaluations make assumptions from the best available data to calculate the effects of a treatment. In an economic evaluation three factors are examined for the intervention treatment and compared treatment option:

- Effect on quality of life
- Effect on life years
- Effect on costs

Chapter 3 shows that thrombectomy leads to improved mRS-scores, which in turn affects all three factors, improved quality of life, life years gained (a longer lifespan) and expected decrease in health and social care costs in the long run, see Figure 4.

This chapter calculates the cost-effectiveness of the thrombectomy intervention, primarily with stent retrievers, as an addition to intravenous thrombolysis in newly detected cases of acute severe ischemic stroke.

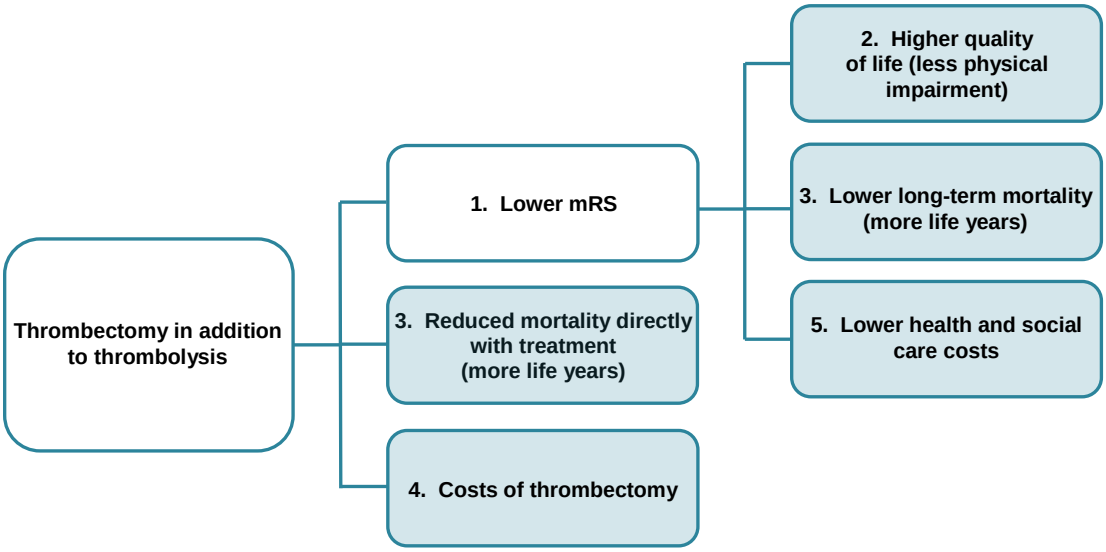

Figure 2. Aspects that affect the economic evaluation

4.2 A model is a complement to studies with patients

Economic evaluations are based on use a model to assess the effects and use of resources (costs) of a treatment over a longer period of time since more data than is available from a single clinical study is often required. A model is used to gather information from a variety of different sources. Using this information then allows assumptions to be made about the probability of different events occurring, such as stroke. Assumptions can then be made about the effect on health and resource use of those events.

Health gain is often expressed as quality adjusted life years, referred to as QALYs. QALYs are a way of estimating health benefits, including effects on life length and quality of life. The results of economic evaluations show the difference between the health benefits and costs for both treatment options.

4.2.1 A number of important assumptions affect the result

Data for the first three months in the five studies have been used for the first year in the model. In the model, a lifetime horizon is used to follow patients. The patients included in the clinical trials were between the ages 65-70 years. The cost-effectiveness analysis is accordingly based on an average patient age of 67 years which corresponds to the average age of the patients in the five studies [1-5].

TLV uses a societal perspective in the model, which means that even costs outside of healthcare are taken into account, see Table 3.

Table 3. Factors influencing the cost-effectiveness analysis

Factors from figure 1	Cost-effectiveness improves the;	Assumptions in the base-case scenario	Source
1. Functional independence	…lower the mRS-score the patient has after stroke.	5 %, 9 %, 5 %, 1 %, -10 %, -8 %	[1-5]
2. Quality of life	…higher the quality of life the patient has after stroke.	see table 4	[38]
3. Life years	…more patients that survive three months after treatment.	4%	[1-5]
	…longer the life expectancy of the patient.	Age at first stroke 67 years	[1-5]
	…the lower the risk ratio of dying the patient has based their mRS-score (increased risk of dying as a result of a stroke). Stroke patients' long-term risk ratio of death.	1,21 1,19 2,11 3,12 4,71 6,03	[39]
4. Cost of thrombectomy	…lower the cost of thrombectomy as an additional treatment.	78 400 kronor*	[40-43]
5. Cost of health and social care	…lower the cost of health and social care.	see table 7	[10, 32]

* Consists of the cost of treatment: medical devices, products, pharmaceuticals, premises, and staff (including on-call and computer tomography staff).

4.3 Less functional impairment gives higher quality of life

Clinical effects measured with the mRS scale describe differences in physical impairment between patients treated with thrombectomy as an additional treatment and the compared treatment option [1-5]. Higher mRS-scores were assigned greater reductions in quality of life [38], see Table 4. These reductions in quality of life and quality of life based on patient age categories [44], see Table 5, are combined to calculate the overall quality of life with the QALY measure.

The risk of a recurrent stroke is assumed to be the same for patients treated with thrombectomy as for patients treated with the comparator. There is no increased risk for another stroke when treating with thrombectomy

compared to thrombolysis. It is therefore assumed that the risk of a recurrent stroke is equal for both treatments.

Table 4. Quality of life reduction according to the mRS-scale [38]

mRS	Quality of life reduction
mRS 0	-0,08
mRS 1	-0,17
mRS 2	-0,25
mRS 3	-0,40
mRS 4	-0,64
mRS 5	-0,75
mRS 6	-1,00

Table 5. Quality of life of different age group [44]

Age groups	QALYs
60 – 69	0,81 (0,79 – 0,83)
70 – 79	0,79 (0,76 – 0,82)
80 – 88	0,73 (0,68 – 0,79)

4.4 Thrombectomy affects life years

The model uses mortality data in several different steps. Mortality after three months is directly linked to thrombectomy treatment [1-5]. The model also used Swedish population data for the base-case risk mortality risk according to age and gender [45]. A risk ratio for stroke patients' risk of death connected to mRS-scores [39] was also used in the model.

4.4.1 More patients expected to survive the first year

The five clinical trials do not show a statistically significant difference in survival three months after stroke in patients who received thrombectomy treatment, but the scientific basis for this conclusion was limited [35]. The clinical studies have, however, 4 percent more patients who survive with thrombectomy treatment after three months [1-5]. This data is used in the model as an assumption for survival during the entire first year, see Table 2.

4.4.2 Life expectancy

TLV has used the average life expectancy of the Swedish population, which is based on data from Statistics Sweden (SCB) [45]. After treatment with thrombectomy, patients on average achieve a lower mRS-score in relation to the comparator [1-5]. A lower mRS-score leads to lower mortality associated with stroke, and more life years [39].

4.5 Costs for thrombectomy as an additional treatment

4.5.1 First-year costs

The costs that have been included in the cost-effectiveness analysis refer to the additional treatment costs for thrombectomy in addition to those for intravenous thrombolysis. Treatment with thrombectomy includes intervention costs, staff costs and other expenses [40, 41]. Since an important factor is that treatment is initiated within a certain time frame, an assumption was made to include on-call expenses in staff costs. An assumption was made that adjusted staff costs for higher on-call expenses 68 percent of the time [46]. Examination costs to assess whether the patient is eligible for treatment with thrombectomy are also included in staff costs [47]. Other costs taken into account for thrombectomy treatment include everything from products for vascular closure, inserting the catheter, tubing, gloves and other consumables [40, 41]. Costs for pharmaceuticals and premises are also taken into account. For the average patient, costs are estimated to be 78,400 SEK [40-43]. Costs for thrombectomy and stroke-related costs are reported in Table 6. The risk of intracerebral haemorrhage is not higher for thrombectomy than for intravenous thrombolysis. Based on these data, it was assumed that the risk and costs for intracerebral haemorrhage are similar for the treatment groups.

The need for health and social care increases the poorer a patients mRS-score is. Health and social care costs for the first year include expenses for follow-up visits, pharmaceuticals, home care and residential care. Swedish costs have been used for TLV's base-case scenario [10] and are distributed according to the mRS scale of 0-5. [32]. These are based on the cost of the first stroke, and eventual recurrent strokes, during the first year.

Health and social care costs are based on Swedish cost data for a general stroke population. Adjustments to increase the costs for health and social care were made using data from the SAHLSIS database in Gothenburg [48], since patients receiving thrombectomy have a more severe stroke than the general stroke population. Subsequently, health and social care costs have been broken down on the basis of severity according to the mRS scale. This is because thrombectomy is used in the treatment of stroke caused by a large blood clot, which implies higher health and social care costs for these patients.

Table 6. Cost of thrombectomy in the first year. (SEK 2015)

Costs for thrombectomy in addition to intravenous thrombolysis [40-43, 47]	**78 400**
Medical devices (catheter, micro catheter, guide wire, and stent retriever)	42 000
Staff (anaesthetists, anaesthetist nurse, neuro-interventionist, nurses, and radiologist. Including on-call staff)	26 700
Other products, pharmaceuticals, and premises	9 700
Health and social care costs for the first year distributed on the mRS-scale [10, 32]	
mRS 0	71 600
mRS 1	94 000
mRS 2	147 200
mRS 3	178 700
mRS 4	233 900
mRS 5	284 700

4.5.2 Lower long-term health and social care costs

Health and social care costs for the following years include, just as for the first year, Swedish costs for return visits, pharmaceuticals, home care and residential care [10]. Unlike the first year, an assumption was made that health and social care costs can be distributed between two groups, mRS 0-3 and mRS 4-5, as the need for care is much greater for the mRS 4-5 [49].

Table 7. Annual costs of thrombectomy after the first year (SEK 2015)

Health and social care costs for the following years, broken down by mRS-scale [10, 49]	
mRS 0 - 3	40 600
mRS 4 - 5	103 900

4.6 Thrombectomy is assessed to be cost-effective based on assumptions made

Based on the five clinical studies, the cost-effectiveness analysis shows that thrombectomy is cost-effective as an additional treatment to intravenous thrombolysis in for acute severe ischemic stroke, see Table 8. In the base-case, the cost per QALY is 45,000 SEK, which is considered to be a low cost per QALY gained.

Table 8. Results of the cost-effectiveness analysis (Costs in SEK)

	Thrombectomy	Thrombolysis	Difference
Treatment effect			
Life years	8,55	7,31	1,24
QALY	3,18	1,97	1,21
Costs			
Total	782 000	727 400	54 600
Cost/ QALY			45 000

TLV's evaluation assumes that the county councils have the same willingness-to-pay for medical devices as for pharmaceuticals within the pricing and reimbursement system. This is broadly consistent with the limits of willingness-to-pay that the National Board of Health and Welfare has reported [50]. Nevertheless, TLV cannot comment on whether this is consistent with the county councils' actual willingness to pay.

4.7 Important to test how different assumptions affect the result

An economic evaluation is always associated with a certain degree of uncertainty and it is therefore important to measure the stability of the results. Assumptions considered in the sensitivity analysis are functional independence, quality of life, life years, cost of thrombectomy, cost of health and social care and the time horizon. The results of the sensitivity analysis are presented below, see also Table 9.

4.7.1 Factor 1 and 2. How quality of life is influenced by a patient's mRS-score

Functional independence measured in five randomised controlled trials

The cost-effectiveness analysis is based on the five studies combined results measured with mRS. A sensitivity analysis was conducted in which patients from each mRS-score were moved to a lower level (applies only for mRS groups 0-4). When this was performed for five and ten percent of the patients, the costs incurred increased respectively to 103,260 SEK and 351,000 SEK per QALY gained.

Quality of life reduction

A sensitivity analysis was also carried out regarding the reduction in quality of life for each mRS level. When the proportion of patients with mRS 0-4 was changed by plus and minus ten percent, the effect on the results was minimal compared with the results of the base-case scenario (46,300 SEK and 43,700 SEK per QALY gained).

4.7.2 Factor 3. Life years

Stroke patients' lifespan is affected by the risk of mortality after treatment, their average age, and a long-term risk ratio for death. Risk of recurrent stroke is also in the base-case scenario and is assumed to be the same for both treatment groups.

Mortality risk after one year

As more stroke patients survive, as a result of treatment with thrombectomy, they gain more years of life which improves the cost-effectiveness. According to the five clinical trials, thrombectomy patients have an absolute difference in survival of four percent. The significance of this difference has been examined by removing patients treated with intravenous thrombolysis from mRS6 and distributing them to other stages of the mRS-scale. The result of this sensitivity analysis show that the cost per QALY gained is 18,400 SEK.

Age of the average patient

The patient’s age when suffering a first stroke affects treatment cost-effectiveness; a higher age is likely to imply fewer life years and therefore fewer QALYs to gain. The base-case assumption for the average patient age is

67 years. In Sweden, however, the average age of stroke patients is 76 years (78 years for women and 73 for men) [51].

Three different sensitivity analyses were performed where the average age was increased by five years, ten years and fifteen years. The results were 66,100 SEK, 97,000 SEK, and 141,900 SEK per QALY gained respectively.

Stroke patient's long-term risk ratio of death

Suffering a stroke contributes to a higher long-term mortality risk. The risk ratio for stroke patients is specific to each mRS-score. This means that patients with mRS-score 0 have a significantly lower risk of death than patients with mRS-score 5. A sensitivity analysis was performed where the risk ratio was equal for all mRS-scores and set to twice the level of a normal population according to age and sex. The results of this sensitivity analysis are that the treatment is more effective at a lower cost, which indicate that the results are cost saving. However, results of a cost-effectiveness analysis indicating that a treatment is cost saving should be interpreted with caution as a model is a simplification of reality.

4.7.3 Factor 4 and 5. Costs

The base-case assumptions of costs are conservative and take into account Swedish prices. Organisational consequences and budget impact within the healthcare sector, such as issues concerning the chain of care and transportation costs between hospitals, are linked to the introduction of thrombectomy as a treatment method. These aspects are important and will be addressed in the second part of the HTA that will be published during 2016.

Direct costs of thrombectomy as an additional treatment

Costs for thrombectomy have been categorised as costs of medical devices and staff as well as other products, pharmaceuticals and premises. In order to take into account variations in the costs of treatment, such as differences in care routines, variations in the cost of medical devices and other cost variations, a sensitivity analysis has been carried out with a reduction as well as an increase of 20 percent of these treatment costs. The outcome of this analysis was a cost of SEK 29,400 and 60,500 respectively per QALY gained.

An important factor of treatment with thrombectomy is that it should occur within a certain time frame. In addition to the direct costs included in TLV's basic scenario, the patient will also need to be transported by ambulance in order to receive treatment in time. Transport costs are not included in TLV's base-case scenario but will be studied further in second of the HTA.

The cost of health and social care

Patients eligible for thrombectomy treatment have usually suffered a much more severe stroke than the general stroke population. This implies that patients can have greater physical impairment, and a higher mRS-score, which a greater need for health and social care. The need for municipal initiatives is greatest for patients with mRS 4 and mRS 4 scores.

The assumption regarding health and social care costs is the single most important parameter in the model, and is the cost that drives the model. In TLV's base-case scenario, health and social care costs were divided between two groups after the first year; mRS 0-3 and mRS 4-5. TLV's base case scenario also used a conservative assumption for health and social care costs based on the Swedish costs of stroke [10].

Since patients with mRS 4 and mRS 5 are considerably more ill and more often in need of special accommodation, there is reason to assume that the cost of health and social care could be higher for these patients than the base-case scenario. The proportion of stroke patients that are eligible for thrombectomy and in need of special accommodations is also uncertain. A sensitivity analysis has thus been performed to calculate an extreme case where all patients with mRS 4 and mRS 5 have significantly higher health and social care costs in comparison with the general stroke population [10]. The analysis used Swedish data for special accommodation costs for the different mRS scores as follows; mRS 0-3 (53,000 SEK), mRS 4 (365,000 SEK) and mRS 5 (600,000 SEK) [52]. The sensitivity analysis showed that the outcome of the cost-effectiveness analysis would result in a cost saving of 239,000 SEK per QALY gained.

TLV will conduct a follow-up of the HTA. The follow-up is planned for spring 2016, when TLV intends to make a further analysis of the health and social care costs of patients treated with thrombectomy.

4.7.4 Time horizon

The base-case assumption is that patients will have lifelong follow-up. A sensitivity analysis was performed to see if the results are affected if the model's time horizon is changed to five years. When the time frame is reduced to five years, the cost per QALY gained is approximately 57,800 SEK.

Table 9. Results of the sensitivity analysis in the cost-effectiveness analysis (SEK 2015)

Factors from figure 1		Assumption in the base-case scenario		New assumption	Result
With basic assumption					45 000
1.	Functional independence	mRS distribution from the five studies		5 % of patients in each mRS level received a poorer mRS-score	103 260
				10 % of patients in each mRS level received a poorer mRS-score	351 000
2.	Quality of life	mRS 0	-0,08		
		mRS 1	-0,17		
		mRS 2	-0,25	+10 %	46 300
		mRS 3	-0,40		
		mRS 4	-0,64	-10 %	43 700
		mRS 5	-0,75		
		mRS 6	-1,00		
3.	Life years	4 % survival at 3 months		No difference in survival at 3 months	18 400
		67 years		+5 years	66 100
				+10 years	97 000
				+15 years	141 900
		Risk ratio for death			
		1,21			
		1,19		Doubled risk ratio	
		2,11			Cost saving
		3,12			
		4,71			
		6,03			
4.	Cost of thrombectomy	78 400 kronor		-20 %	29 400
				+20 %	60 500
5.	Cost of health and social care	mRS 0-3		53 000	Cost saving
		mRS 4		365 000	
		mRS 5		600 000	
6.	Time horizon	Life-time		5 years	57 800

4.8 Validation of the cost-effectiveness analysis

TLV has validated the economic model used in the cost-effectiveness analysis. The validation process involved TLV reviewing the model structure and its input parameters. A recently published scientific study in which the cost-effectiveness of thrombectomy was studied a population in the UK was used for this [53]. TLV has also had access to an HTA from Region Skåne, which is an assessment of thrombectomy with Swedish context, which also includes a cost-effectiveness analysis [54]. During the work process,

communication has taken place with the working group in Region Skåne. TLV has also collaborated with the National Board of Health and Welfare concerning the results of the clinical trials. TLV has also had access to an unpublished economic model to validate results. Furthermore, TLV has reviewed this model to examine similarities and differences and compared it with our results.

Individual parameters and the plausibility of various assumptions have been discussed and the dialogue with the modeller has been continuous during the working process. TLV has chosen to consistently use conservative assumptions in order not to over-estimate effects or under-estimate costs.

Validation work consisted of conducting own searches, seeking alternative data and utilising medical expertise. TLV has evaluated and adjusted the model in order for it to be based on the best available data. For example, the costs of intervention (treatment) have been adjusted and now include a more expensive set of material costs than in the first base-case scenario. The adjustment was made in consultation with medical experts and after that the parameters in the published scientific study had been studied.

staff costs have also been adjusted regarding the number of persons and time estimates. With regard to staff costs, on-call costs have now been included in TLV's base-case assumption. Even the mortality risk has been adjusted in order to better reflect the risks for stroke patients after completion of thrombectomy treatment by distributing the risk over different mRS-scores.

The validation process includes carrying out sensitivity analyses where TLV examines the uncertainty of the results. For the clinical efficacy data on which the basic assumption was based, TLV has for example, chosen to perform a sensitivity analysis in which the effect was adjusted. The selected age in the basic assumption is consistent with the clinical trials, and TLV has chosen to carry out a sensitivity analysis in which the age is slightly higher. This was done to better reflect the age when Swedish patients suffer a stroke. TLV also did a sensitivity analysis for the costs of health and social care.

4.9 Conclusions

The results show that thrombectomy is highly likely to be a cost-effective treatment for acute severe ischemic stroke. TLV's base-case scenario resulted in a low cost per QALY gained. The proportion of patients with a stroke that is suitable for thrombectomy and the need for special accommodation remains uncertain. A sensitivity analysis was therefore performed to calculate an extreme case where all patients with mRS 4 and mRS 5 have significantly higher health and social care costs in comparison with the general stroke population. The results of this analysis showed that health and social care costs have a great impact on the result and imply that the results should be cost saving.

TLV's base-case scenario uses clinical efficacy results from five clinical trials. Changes in assumptions about the clinical efficacy, such as when the mRS-score changed, had a great impact on the result. Sensitivity analyses showed that treatment with thrombectomy was at best, cost saving and the estimated maximum cost per QALY gained was 351,000 SEK.

TLV has assumed that there is the same willingness to pay willingness-to-pay for medical technologies that has been used for pharmaceuticals in the pricing and reimbursement system. TLV therefore deems that the cost-effectiveness ratio is within the accepted willingness-to-pay. Nevertheless, TLV cannot say if this is consistent with the county councils' actual willingness to pay.

In the second part of the HTA, TLV will follow-up the cost-effectiveness analysis by investigating aspects associated with health and social care organisational consequences and budget impact, as well as relevant ethical issues. The second part of the HTA will be published before the summer of 2016.

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