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Cost-effectiveness of stent-retriever thrombectomy in large vessel occlusion strokes of the anterior circulation: analysis from the French societal perspective

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ABSTRACT

Objectives: To determine the cost-effectiveness of stent retriever thrombectomy (SRT) added to standard of care (SOC) in large vessel occlusion (LVO) strokes, adopting the French societal perspective given the lack of published studies with such perspective.

Methods: We developed an hybrid model (decision tree until one year post-stroke followed by a Markov model from one year onward). The time horizon was 20 years. We calculated transition probabilities across the modified Rankin Scale (mRS) based on a published meta-analysis. The main outcome measure was quality adjusted life-years (QALYs) gained. Resources and input costs were derived from a literature search. We calculated the incremental cost-effectiveness ratio (ICER) expressed as cost/QALY. We used 1-way deterministic and probabilistic sensitivity analysis (PSA) to evaluate the model uncertainty.

Results: In the base-case, adding SRT to SOC resulted in increased effectiveness of 0.73 QALY while total costs were reduced by 3,874€ (ICER of -5,400€/QALY). In the scenario analysis adopting the French healthcare system perspective, the ICER was 4,901€/QALY. Parameters the most influential were the relative risks of SRT over SOC for 90-days mortality and for 90-days mRS 0-2, and the time horizon. PSA showed the 95% confidence interval of the ICER was -21,324 to 4,591€/QALY, with SRT having 85.5% chance to be dominant and 100% to be cost-effective at a threshold of 50,000€/QALY.

Conclusion: SRT was dominant from a French societal perspective, from 9 years post-stroke onwards. Cost-effectiveness of SRT added to SOC becomes undisputable with evidences from payer and societal viewpoints.

Keywords: cost-effectiveness; cost-utility analysis; stent retriever; stroke; thrombectomy; tissue type plasminogen activator

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3 INTRODUCTION

Acute ischemic stroke (AIS) is a leading cause of disability in industrialized countries and is the third cause of death worldwide [1]. AIS remains a public health issue given its socio-economic impact in terms of substantial acute care costs together with its burden related to residual disability with 75% of people presenting neurological sequelae and 25% loss of independence [2]. In France, the economic burden of stroke was estimated at 8.3 billion € for Year 2009 [3].

In eligible ischemic stroke patients, intravenous (IV) thrombolysis with tissue plasminogen activator (t-PA) has remained the mainstay of treatment of AIS over the last two decades [4,5]. Given the modest benefit of IV t-PA in AIS caused by large vessel occlusions (LVO) [6], endovascular treatment with mechanical thrombectomy devices has been tested but initially showed disappointing results [7–9]. More recently, second-generation devices represented by stent-retrievers have demonstrated their effectiveness in significantly improving functional outcomes [10]. Stent-retriever thrombectomy (SRT) added to IV t-PA is now a Class I, Level of evidence A recommendation in AIS with causative occlusion of the internal carotid artery (ICA) or middle cerebral artery (MCA) segment 1 (M1) within 6 hours after symptoms onset [11,12], this applies to a maximum of 10% of AIS patients in clinical practice.

Owing to the economic impact of SRT, several economic evaluations have been conducted and demonstrated that SRT was cost-effective or even cost-saving, this include one recently published in France [13,14]. Of these, only one, conducted outside France (USA), adopted a societal perspective [15] which did not adequately accounted for medical resource consumptions induced as a result of stroke generating disabilities and loss of independence. For example, that study did not include indirect costs such as productivity losses or costs related to caregivers.

Our study aimed to evaluate the cost-effectiveness of SRT added or not to IV t-PA in AIS secondary to LVO, compared to IV t-PA alone from a fully comprehensive societal perspective, as recommended by the French Health Technology Assessment, *Haute Autorité de Santé* [16].

4 METHODS

4.1 Overview

We performed a cost-utility analysis comparing SRT added or not to IV t-PA in AIS secondary to LVO, to IV t-PA alone. We adopted a French societal perspective which is the

broadest one accounting for all possible incurred costs including those from patients, communities/local organizations, and healthcare systems. Our target population was people with AIS secondary to LVO confirmed by imaging, and eligible for mechanical thrombectomy. At inclusion, the mean age was 67.3 years with a 1:1 male/female ratio [10]. We considered a lifetime time horizon of 20 years based on French population life expectancy at this age (INSEE 2017). In the absence of long-term outcomes reported in the literature, we modelled lifelong costs and clinical outcomes including quality of life.

4.2 Model structure

We developed an hybrid model comprising three clinical stages consistent with the natural course of patients with stroke [17]. The first phase was from stroke onset until 90 days after (rapid rehabilitation), the second was from 90 days until one year post-stroke (slower rehabilitation), and the third was from one year post stroke onwards (**Fig. 1**). The two first stages were modelled with a decision tree while the long-term phase consisted in a Markov model applying one year cycles. We built up our model with TreeAge software (TreeAge Pro 2016, version 16.1.1.0; TreeAge, Williamstown, MA).

In each stage, patients were distributed in three health states according to their disability as measured by the modified Rankin Scale (mRS) which is the commonly used scale measuring the degree of dependency in the daily activities of patients after stroke (0: no disability; 6: death). These three health states were functional independence (mRS 0-2), presence of permanent disability (mRS 3-5), and death (mRS 6). At each cycle, patients could remain in the same health state, or decline towards disability or transition to death.

4.3 Model assumptions

We made four main assumptions for the purpose of modelling. First, patients could recover from their disability (i.e. transition from mRS 3-5 to mRS 0-2) only during the first year post-stroke while from one year post-stroke onwards, patients could either remain in the same state or decline to a less favorable state (either mRS 3-5 or mRS 6) [17]. Secondly, based on our clinical experts' opinion (B.G. & F.T.), we assumed the rate of LVO-AIS recurrence retreated with SRT to be null owing to its very rare onset. Moreover, in our Markov model, recurrences were included into our transitional probabilities with the same yearly rate [18] and considering only one recurrence per cycle. Thirdly, we did not include treatment adverse effect as the rate of intracerebral hemorrhage which was identical in each group (SRT vs IV t-PA: relative risk [RR] 1.11 CI95% 0.67 to 1.82) [10]. Last, in the absence

of long-term data about SRT, after 90 days, we assumed the evolution of patients in both groups (SRT versus IV t-PA) to be solely dependent of their health state (independent, dependent or death) as presented in **Table 1**.

4.4 Model input parameters

Where possible, we used inputs from individual patient data. Otherwise, we performed a literature search to obtain the most accurate estimates for short and long-term clinical outcomes, epidemiological data, utilities, resources and costs. The clinical relevance of our parameters was cross-checked by our clinical experts. Main inputs used in the model are detailed in **Table 1**.

4.4.1 Transition probabilities

Short-term (up to 90 days) outcomes were obtained from a published systematic review with meta-analysis of six RCTs that included 1673 patients in total [10]. Mid-term outcomes were based on individual patient data from the *AVC69* study which is a large French regional cohort of 673 stroke patients enrolled between 2006 and 2007. In the absence of available French data, we used long-term outcomes, from 12 months onwards, reported in a published Canadian cost-utility analysis [19], which was based on results from a British cohort (Oxford Vascular Study) of 618 stroke patients included between 2002 and 2007.

Finally, in addition to stroke-specific mortality, we applied an all-cause mortality multiplier using age-specific mortality tables extracted from the general French population database (INSEE 2015).

4.4.2 Costs

In line with the choice of a societal perspective, stroke costs were categorized into three groups: 1)- direct medical costs (initial hospital stay, cost of the procedure and of the stent, recurrent hospital stay, rehabilitation hospital stay, medical and paramedical visits, secondary prevention medication, biological tests); 2)- direct non-medical costs (professional and informal [« proxy good method » valuing time spent by a family member or a close friend as if they were replacing a professional caregiver] caregivers and institutions for elderly persons); 3)- indirect costs (patients productivity losses with a professional activity according to the friction cost method).

We decided to exclude published studies on stroke costs in France which were deemed to be outdated or irrelevant [20–22]. We therefore estimated each cost category from hypothesis

based on clinical guidelines. Some resource consumptions were not considered such as technical aids, and occupational therapists, due to the absence of published data or data deemed too inaccurate. We also excluded pre-hospital transfer costs as our model started at the hospital admission of stroke patients. Except acute costs which were estimated according to the therapeutic strategy, subsequent costs were estimated according to the level of disability.

Early-death costs (≤ 90 days post-stroke) were estimated using mean annual costs reported of by Chevreur et al. [23] while for mid-term and late-death costs (>90 days post-stroke onwards), we accounted only cumulated costs during previous phase according to the level of disability.

All included costs are presented in **Appendix 2**. Costs were expressed in euros (€) and were based on reference sources of the French market (salaries, devices, medical visits, drug prices) applicable to Year 2016. Costs extracted from literature were inflated to Year 2016 using the appropriate Consumer Price Index then converted in euros (€) according to OECD recommendations.

4.4.3 Utilities

In the absence of relevant French data, we used utility values from the OXVASC cohort [24] which were calculated from EQ-5D questionnaires distributed to transient, ischemic or hemorrhagic stroke patients at 1, 6, 12, and 24 months post-stroke. We assumed that utilities obtained at one month were similar to those at three months, as data at three months were unavailable. This choice was conservative as physical rehabilitation usually improves significantly and rapidly until three months post-stroke. Moreover, EQ-5D scores at 90 days were adjusted to the number of patients in each mRS score from our meta-analysis [10] on a prorata basis, in order to obtain more plausible estimates for each mRS. EQ-5D scores were then converted into QALY by multiplying the score with the number of month spent in each health state. Utilities used in the model are detailed in **Table 1**.

4.5 Base-case and sensitivity analyses

We calculated the incremental cost-effectiveness ratio (ICER) which was expressed as costs per quality-adjusted life-years gained (€/QALY). We presented a discounted ICER which was obtained applying a 4% annual discount rate to costs and outcomes according to French guidelines [16]. In the absence of formal threshold defined in France, we arbitrarily chose a willingness-to-pay (WTP) at 50,000€/QALY.

We conducted two scenario analyses (**Appendix 3**). First, we used transition probabilities up to 90 days obtained from the French THRACE RCT [25]. Second, we adopted the French Healthcare perspective to allow indirect comparisons with other published studies [13] and external validation of our model.

We undertook a one-way deterministic sensitivity analysis for all parameters in order to assess the impact that a fixed change in each parameter has on the ICER (**Table 2**), these were presented in a Tornado diagram. The range used for each parameter was the 95%CI for transitional probabilities and utilities. We made a sensitivity analysis on mid-term costs for different length of stay at the rehabilitation hospital, and on long-term costs based on the opportunity cost approach for informal care. Discount rate tested for sensitivity analysis were 3% and 5%.

Finally, we conducted a probabilistic sensitivity analysis (PSA) using second-order Monte Carlo simulations (10,000). The PSA included the variables which were deemed the most influential from visual inspection of the Tornado diagram. The distribution used was Dirichlet for probabilities and lognormal for relative risks (RR). Owing to our method of calculation for incurred costs, we had to use a triangular distribution to costs applying for each parameter a likeliest, minimum, and maximum value as in the deterministic sensitivity analysis.

5 RESULTS

5.1 Base case and scenario analyses

In the base-case analysis, SRT was dominant over IV t-PA alone at it displayed 0.73 additional QALY while reducing total costs by 3,874€ (**Table 3**).

In the scenario analysis using the clinical effectiveness estimates from the THRACE RCT, SRT was still dominant over IV t-PA alone (+0.45 QALY; -1,750€ total incremental costs).

In the scenario analysis adopting the French healthcare system perspective, SRT generated 0.71 additional QALY while increasing total costs by 3,516€, leading to an ICER of 4,901€/QALY which is deemed cost-effective under our pre-defined WTP.

5.2 Sensitivity analyses

One-way sensitivity analyses (**Fig. 2**) showed the most influential parameters on the ICER were the 90-days mortality rate, the time horizon, the 90 days mRS, and long-term cost of dependent patients. For each of these variables, the ICERs remained way below our

defined WTP. The change on time horizon showed that SRT was dominant from 9 years on post-stroke (**Table 4**).

Based on the PSA (**Fig. 3**) using eight selected parameters (of which seven generated ICER variations higher than 5,000 €/QALY plus one we added for long-term costs of independent patients), the 95%CI of the ICER was -21,324 to 4,591 €/QALY. The probability of SRT being dominant was 85.5%, while the probability of SRT cost-effective was 100% under a 50,000 WTP (**Appendix 1**).

6 DISCUSSION

Our study showed that SRT was dominant, being less costly and more effective than IV t-PA alone, from the French societal perspective. Although total costs with SRT were higher during the first year after stroke, this was offset from Year 2 onwards and over a long-term period total costs with SRT became lower. SRT was cost saving from a societal perspective and improved quality of life outcomes, which is consistent with the large and well-demonstrated clinical effectiveness benefit observed 90 days after stroke. Using the healthcare system perspective, SRT was cost-effective (more costly and more effective than IV t-PA alone). The different results according to the choice of perspective emphasizes that the societal approach is essential because it affects total long-term costs of this condition with long-term disabilities.

Our main results were consistent with other published economic evaluations of second-generation devices which were conducted in other country settings, namely USA, Canada, UK and Sweden [13]. Of these, three studies showed that SRT was a dominant strategy while four concluded that SRT was cost-effective with ICERs found below conventional WTP thresholds. The parameters identified in other studies as having a significant impact on ICER [13] have been found to be highly influential in our cost-utility analysis, at exception of the procedural costs and utilities for dependent patients. As in the study by Xie et al. [19], the time horizon had a significant impact on ICER (13,069 €/QALY at 5 years and increased to 99,277 €/QALY at 1 year).

Our study has several strengths. Our analysis was conducted in accordance with the French guidelines [16], mentioned also in European recommendations from *European Network for Health Technology Assessment* (EUnetHTA) [26]. Both deterministic and probabilistic sensitivity analyses showed the robustness of our findings. These have included worst-case scenarios using the most pessimistic value of effectiveness variables (RR of mRS 0-2 at 3 months and RR of death). Under these scenarios, the impact on the ICER was minor

and showed SRT largely remaining cost-effective (ICER <2,000€/QALY). Such analyses are important to consider given that "real-life" outcomes are often less favorable compared to those seen in RCTs. Secondly, we used robust clinical effectiveness inputs from a systematic review with meta-analysis of 6 RCTs [10]. Transition probabilities were obtained from individual patient data extracted from a comprehensive multicenter cohort study in the Rhône department of France (AVC69 study). Besides, even if we did not use costs extracted from French studies because they were outdated [20,21] or did not report costs from a societal point of view [22], we estimated costs based on French clinical pathway and resources, valued with French costs. Also, we did compare our costs to those from a French study that evaluated total healthcare costs at one year post-stroke at 20,235€ [22], that are consistent with the costs integrated in our model. Moreover, our costs estimations were in line with European studies, that evaluated costs associated with stroke from a societal perspective (mean cost at one year post-stroke: 19,953€ ± 18,114€ in Italy [27], 21,200€ in Sweden [28]). However, comparisons with other countries must be cautious as medical and non-medical resources vary significantly from a country to another, and also, in cost-of-illness studies, the economic approach is different.

Thirdly, the choice of a societal perspective, which was justified given the importance of direct non-medical costs (more than 75% of total costs 1 year after stroke), allowed to fully reflect the socio-economic burden of stroke in France. This seems of even greater importance given that the proportion of young patients sustaining a stroke had strongly increased between 1985 and 2011 [29].

There are some limitations to this study. First, the choice of a three health state model, which was made according to best available data, can be seen as a simplification of the clinical pathway. The costs could be different depending on the mRS status among dependent patients [30]. In their study conducted alongside with SWIFT PRIME RCT, Shireman et al. [30] estimated annual hospital costs of USD 21,618 (based on 2015 costs) for mRS 3 patients, of USD 43,755 for mRS 4 patients, and of USD 64,327 for mRS 5 patients. Secondly, our choice of data input within the model could be discussed. Owing to the lack of available studies, we used data from studies conducted outside France to describe long-term transition probabilities, utilities and costs. Moreover, except for effectiveness parameters, data sources did not strictly correspond to our target population which was people with AIS secondary to LVO, eligible for mechanical thrombectomy.

Finally, this study did not account for some costs such as those related to the transfer of patients for SRT, the infrastructure for SRT procedure, home adjusting costs, and technical

aids costs. As a result, we may have under-estimated total costs in our model, which was conservative.

In conclusion, we showed that SRT was a dominant strategy from a French societal perspective and was also cost effective from the healthcare system perspective which is consistent with another cost-utility analysis [31] and with the decision by the French Health Technology Assessment body to recommend SRT for reimbursement made in 2016 [32]. While SRT is the gold standard in the treatment of LVO strokes, other modern thrombectomy devices with direct aspiration first pass technique (ADAPT) seems to be an interesting alternative [33,34]. Further research is needed to determine the best first-line approach. Finally, while significant technological improvements have been made on thrombectomy devices and now that the clinical effectiveness of newer mechanical thrombectomy is widely demonstrated, the accessibility to this breakthrough technology remains an issue. Data from regional cohorts suggest that only one quarter of eligible patients do get offered this procedure [35]. This is why the improvement of acute stroke care organization represents a major stake. Within this scope, strategies of care pathways, such as drip-and-ship or direct transfer to comprehensive stroke center (mothership) must be evaluated by prospective randomized controlled trials to define which one is the most beneficial to patients depending on regional organizations [36,37] (appendix 4).

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TABLES

Table 1. Base-case values related to patients' outcomes

Model inputs	Base-case values	CI 95%	Reference	
Probabilities for each health state at 90 days after stroke with IV tPA alone				
mRS 0-2	0.323	0.2326-0.3695	[10]	
mRS 3-5	0.505	0.4663-0.5797		
mRS 6	0.17	0.1435-0.2063		
Relative risks (SRT + IV tPA vs IV tPA) for health state at 90 days after stroke				
mRS 0-2	1.56	1.36-1.79	[10]	
mRS 3-5	-	-		
mRS 6	0.85	0.67-1.07		
Transitional probabilities at 1 year after stroke				
Independent to				
Independent mRS 0-2	0.9118	0.7332-0.99	AVC69 cohort ^a	
Dependent mRS 3-5	0.0824	0.0395-0.1253		
Death mRS 6	0.0059	0-0.088		
Dependent to				
Independent mRS 0-2	0.0862	0.0127-0.1597		
Dependent mRS 3-5	0.8362	0.7725-0.8999		
Death mRS 6	0.0776	0-0.2132		
Transitional probabilities past 1 year after stroke				
Independent to				
Independent mRS 0-2	0.9832	0.9340-0.98	[19,38]	
Dependent mRS 3-5	0.0134	0.0127-0.0141		
Death mRS 6	0.0034	0.0032-0.0036		
Dependent to				
Independent mRS 0-2	0	0		
Dependent mRS 3-5	0.9904	0.9409-1		
Death mRS 6	0.0096	0.0091-0.0101		
Utilities				
At 90 days	EQ-5D mRS \leq 2	0.787	[24]	
	EQ-5D mRS 3-5	0.337		
At 1 year	EQ-5D mRS \leq 2	0.8114		
	EQ-5D mRS 3-5	0.4893		

CI = confidence interval; EQ 5D = EuroQol 5 dimensions; IV= intravenous; mRS= modified Rankin scale; SRT= stent retriever thrombectomy; t-PA= tissue plasminogen activator.

^aUnpublished data, 2007, obtained from A-M.S.

Table 2. Ranges used for each parameters in the one-way sensitivity analyses

Parameters		Lower value	Upper value
Time horizon (years)		2	30
Discount rate (%)		3	5
Probabilities for each state	At 90 days	see Table 1	
	90 days to 1 year		
	1 year		
Utilities for independent state (EQ-5D)	0-90 days	0.1841	0.2097
	90 days-1 year	0.6012	0.6160
	1 year	0.8016	0.8213
Utilities for dependent state (EQ-5D)	0-90 days	0.0577	0.1109
	90 days -1 year	0.3418	0.3922
	1 year	0.4557	0.523
Costs 8-90 days ^a (€)	Independent state	6,595	11,894
	Dependent state	10,145	18,064
Costs after 1 year ^b (€)	Independent state	3,701	6,333
	Dependent state	11,715	18,895

EQ 5D = EuroQol 5 dimensions.

^aCosts 8-90 days: costs corresponded to the 95%CI of the length stay in rehabilitation hospital which was between 26 and 80 days.

^bCosts post 1 year: opportunity cost approach calculated from mean wage of a French worker (14.52€/h net in 2016)

Table 3. Results of the base-case analysis and scenario analyses

	Total costs	Incremental costs	Total QALYs	Incremental QALY	ICER
Base-case analysis					
IV t-PA	127,503		5.27		
SRT	123,629	-3,874	5.98	0.73	-5,400
Scenario 1: Using clinical effectiveness inputs from the THRACE randomized controlled trial					
IV t-PA	126,136		5.9		
SRT	124,386	-1,750	6.35	0.45	-3,924
Scenario 2: Adopting the French healthcare perspective					
IV t-PA	48,795		5.27		
SRT	52,311	3,516	5.98	0.71	4,901

ICER = Incremental Cost-Effectiveness Ratio; IV= intravenous; QALY= Quality Adjusted Life Years; SRT= stent retriever thrombectomy; t-PA= tissue plasminogen activator.

Table 4. Results of one-way deterministic sensitivity analysis on time horizon and discount rate

	Parameters	ICER (€/QALY)
Base-case analysis	20 year time horizon and 4% discount rate	-5,400
Time horizon (number of years)	2	16,393
	5	106
	10	-4,624
	15	-5,518
	30	-3,632
Discount rate (%)	3	-5,770
	5	-5,023

ICER= Incremental Cost Effectiveness Ratio; QALY= Quality Adjusted Life Years.

FIGURES

Fig 1. Model structure. Decision analytic tree and Markov state transition model. A patient enters the model when admitted to hospital for acute ischemic stroke and receives either intravenous tissue plasminogen activator with or without stent-retriever thrombectomy. At each cycle, patients could remain in the same health state, or decline towards disability or transition to death. *AIS= acute ischemic stroke; IV= intravenous; mRS = modified Rankin Scale; SRT= stent retriever thrombectomy; t-PA= tissue plasminogen activator.*

Fig 2. One-way sensitivity analyses: Tornado diagram. Effect of parameter variation on the incremental cost-effectiveness ratio using SRT in addition to IV t-PA. Dark bars represents the lower bound, light bars represents the upper bounds. *ICER= incremental cost-effectiveness ratio; IV= intravenous; SRT= stent retriever thrombectomy; t-PA= tissue plasminogen activator.*

Fig 3. Probabilistic sensitivity analyses. Incremental cost-effectiveness scatter plot of patients treated with SRT in addition to IV t-PA versus IV t-PA alone. Dotted line represents an incremental cost/QALY of 50,000 WTP. Each dot represents a simulation run (1,000 iterations). *WTP = willingness-to-pay.*





