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Economic analysis of the first pass effect in mechanical thrombectomy for acute ischemic stroke treatment in Spain.

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Abstract

Objective: The mechanical thrombectomy (MT) benefit is related to the degree of reperfusion achieved. First Pass Effect (FPE) is defined as complete/near revascularization of the large vessel occlusion (modified Thrombolysis in Cerebral Infarction (mTICI) 2c-3) after a single device pass. This study assessed the health benefit and economic impact of achieving FPE for acute ischemic stroke (AIS) patients from the Spanish National Health System (NHS) perspective.

Design: A lifetime Markov model was used to estimate incremental costs and health outcomes (measured in quality-adjusted life-years [QALY]) of patients that achieve FPE. A sub-analysis of the STRATIS registry was performed to obtain clinical outcomes. The base-case included all patients that achieved at least a final mTICI≥2b, while the alternative scenario included all patients regardless of their final mTICI (0-3). Treatment costs were updated to reflect current practice based on expert panel consensus, while other acute and long-term costs were obtained from a previous cost-effectiveness analysis of MT performed in Spain. Sensitivity analyses were performed to assess the model's robustness.

Setting: Spanish healthcare perspective.

Participants: AIS patients in Spain.

Interventions: FPE following MT.

Outcome measures: The model estimated QALYs, lifetime costs and net monetary benefit (NMB) for the FPE and non-FPE group, depending on the inclusion of reperfusion groups and formal care costs.

Results: STRATIS sub-analysis estimated significantly better clinical outcomes at 90-days for the FPE group in all scenarios. In the base-case, the model estimated lifetime cost-saving per patient of €16,583 and an incremental QALY gain of 1.2 years of perfect health for the FPE

group. Cost-savings and QALY gains were greater in the alternative scenario (-€44,289; 1.75). In all scenarios, cost-savings were driven by the long-term cost reduction.

Conclusion: Achieving FPE after MT can lead to better health outcomes per AIS patient. and important cost-savings for the Spanish NHS.

Article Summary

Strengths and limitations of this study

- A Markov model estimated the lifetime health and cost implications of achieving FPE in AIS patients treated with Mechanical Thrombectomy in Spain from the NHS perspective.
- The model allows to quantify the benefits of aiming mechanical thrombectomy techniques that may increase the first pass effect success rates.
- A limitation of this study is that clinical efficacy and patient characteristics were based on the STRATIS registry, which included centers outside Spain.
- Another limitation is that some model parameters, such as acute and long-term costs have been derived from literature, which have been validated by clinical experts.

INTRODUCTION

The annual number of strokes in the European Union is forecasted to increase by 34% in 2035, mainly due to its aging population. With improving survival rates after stroke, almost 1 million more people will be living with a stroke as a chronic condition, rising from 3.7 million in 2015 to 4.6 million in 2035 (1). It is estimated that the incidence and prevalence of strokes will increase by 35% and 31% respectively in Spain by 2035 (2), which will inevitably raise the associated economic burden.

Mechanical thrombectomy (MT) is the most effective reperfusion treatment used in acute ischemic stroke (AIS) management in patients with large vessel occlusion (LVO) (3,4). Its cost-effectiveness has already been demonstrated in Spain; improving functional outcomes is associated with a higher quality of life and reduced health costs, leading to €44,378 in savings per patient compared to thrombolysis with intravenous tissue-type plasminogen activator (IV-tPA) alone (5).

Clinical evidence suggests that the number of passes during a MT inversely correlates with the functional outcome of the procedure (6,7). Achieving complete/near revascularization of the LVO (modified Thrombolysis in Cerebral Infarction [mTICI] 2c-3) after a single pass with MT, known as first pass effect (FPE), is associated with significant improvements in clinical outcomes and can be considered an independent predictor of good functional outcomes (8). Recent studies have begun to try to identify factors or predictors of first pass effect which may impact the choice of thrombectomy device and technique in the future (8–11).

The objective of this study is to assess the health outcome benefits and economic impact of achieving FPE for the AIS patients from the National Health System (NHS) perspective in Spain.

METHODS

Model structure

A previously published cost-effectiveness model comparing MT + IV-tPA with IV-tPA alone in a Spanish NHS setting was modified to reflect only patients that received MT treatment which afterwards were stratified to reflect those who achieved FPE and those who didn't (Non-FPE) (5), and allowed to estimate lifetime health and costs outcomes of the two patient groups. As in the previous modelling, this analysis is also over the patient's lifetime and from the Spanish NHS perspective. The model was developed using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA).

The model had a two-phase structure, consisting of an acute-subacute phase from stroke onset to 90 days, and a rest-of-life phase 91 days after stroke to the end of patient's life. In the acute-subacute phase, patients enter the model once reperfusion status (FPE vs Non-FPE) has been determined, and then are assigned to one of the seven mutually exclusive health states based on Modified Ranking Scale (mRS; 0-no symptoms, 6-death) to reflect several degrees of disability at 90 days. Afterwards, patients enter a Markov structure, from 91 days after the stroke to the end of the patients' life. In this phase, patients could remain in the same health state or transition to different states during each annual cycle until the end of life, depending

on the occurrence of a recurrent stroke or death from other causes (age-gender specific mortality). A half-cycle correction was used to account for transitions occurring in the middle of a cycle.

Patient population

The model simulates a hypothetical cohort of 1,000 patients with clinic-demographic characteristics based on the STRATIS registry (Systematic Evaluation of Patients Treated With Neurothrombectomy Devices for Acute Ischemic Stroke) (12). The base-case analysis stratified patients into FPE and Non-FPE groups considering STRATIS registry patients that achieved a final mTICI≥2b. The alternative scenario included all STRATIS registry patients regardless of their final mTICI (0-3).

Clinical data

Clinical data was obtained from a sub-analysis of the STRATIS registry (12) in which FPE and Non-FPE groups were compared. Moreover, it was considered that patients were at risk of experiencing adverse events (symptomatic intracranial hemorrhage and malignant cerebral edema) during the acute-subacute phase, therefore adverse events data was also obtained from STRATIS registry sub-analysis.

Categorical variables were compared using $\chi 2$ (Chi-square) test and Mantel-Haenszel Chi-square test when appropriate. Proportion differences were compared by z-test both one-sided and two-sided tests are performed (considering 5% and 2.5% significance level respectively). All statistical analyses were performed using SAS version 9.4.

Background age-gender related mortality was obtained from the latest available Life Table in Spain (data from 2018) (13) and relative risks of death by mRS score were used to adjust age-gender-related mortality (14) to account for the increased risks observed among stroke survivors (Supplementary Material Table A1 & A2). Recurrence stroke rates were obtained from Mohan et al. (15) (Supplementary Material (Table A3).

Quality of life

Health outcomes were measured using quality-adjusted life years (QALY), a measure that weights life-years gained with an intervention by its utility value. Utilities assigned to health states can take values from 0 (death) to 1 (optimal health) and negative values (state worse than death). Utilities by mRS score were obtained from Rivero-Arias et al. 2010 (16), with values ranging from 0.93 (mRS 0) to -0.54 (mRS 5) (Supplementary Material (Table A4).

Costs

The study considered the Spanish NHS perspective, consequently, only direct medical costs were considered, including treatment and adverse events management costs, acute and long-term care costs. Treatment costs were updated to reflect the costs for each patient group (FPE vs Non-FPE) and were kept in line with the new treatment approaches according to local practice based on a panel of experts' consensus. Treatment costs in both groups FPE and Non-FPE included the costs of AIS diagnosis, and adjunctive IV-tPA in 30% of the cases according to local practice (Table A5, Supplementary Material).

Adverse events, acute and long-term costs by mRS score were kept consistent with the previous model (5). For each scenario, a second analysis was performed to include formal care costs such as nursing/residential costs. All costs are presented in Euros and were inflated to reflect

Euros in 2020 (Table 1). Costs and health outcomes were discounted at an annual discount rate of 3% consistent with the relevant health technology assessment guidelines for Spain (17).

Table 1. Adjusted Acute and long-term costs (Euros 2020)

mRS	Acute costs	Annual long-term cost	
	Total Acute care cost (€)	**Total Long-term healthcare cost (without nursing and residential care cost) (€)**	**Total including nursing and residential care cost (€)**
mRS 0	4,718	1,340	2,767
mRS 1	5,242	1,489	3,074
mRS 2	5,766	1,638	3,382
mRS 3	6,468	23,250	33,061
mRS 4	7,187	25,833	53,339
mRS 5	7,906	28,417	67,400
mRS 6	4,046		

Note: Table adapted from De Andrés-Nogales et al., 2017 (6)

Economic model outcomes and sensitivity analysis

The model estimates the lifetime total costs and QALYs for each patient group. To quantify the net economic value of FPE, the net monetary benefit (NMB) was calculated, considering a willingness-to-pay (WTP) threshold of €30,000/QALY, (NMB=(Incremental QALYs×WTP)-Incremental Costs) (18,19).

Deterministic Sensitivity Analysis (DSA) and Probabilistic Sensitivity Analysis (PSA) were conducted to evaluate results' robustness (20). DSA assigns a one-way variation to input parameters including discount rates, mRS at 90 days, age, health states utilities, recurrent stroke rates, relative risk of death, and all costs (treatment, acute and long-term costs). In PSA, 10,000 Monte Carlo simulations were run after assigning a probability distribution to all key

parameters simultaneously (mRS scores at 90 days (Dirichlet), mortality relative risks (Lognormal), starting age (Normal), utilities (Beta) and costs (Gamma)), to account for the general uncertainty around model inputs (5).

Patient and public involvement

This study was conducted without patient and public involvement. Therefore, patients were not involved in the study design, reporting or interpretation of the findings. This study included a post-hoc analysis of an existing study, therefore institutional review board approval was not obtained for this analysis. Moreover, no research approval was required for model input parameters that were obtained from literature or based on panel of experts consensus.

RESULTS

Based on STRATIS sub-analysis, the mean age of stroke considered in the model was 68 years. Both groups have similar characteristics at baseline. Descriptive statistics on the FPE and Non-FPE groups are reported in Supplementary Material, Tables A6-A7-A8-A9.

Our results suggest that the FPE group had significantly better clinical outcomes at 90 days after stroke compared to the Non-FPE group in the base-case scenario (mRS 0-2: 66.2% vs 54.6%, p-value<0.005). Similar results in the alternative scenario were observed (mRS 0-2: 66.9% vs 50.6%, p-value<0.0001) (Figure 1). Adverse events results across scenario populations are presented in the Supplementary Material (Table A10).

[Insert Figure 1]

In the base-case scenario, the model estimates an average lifetime cost per patient equal to €97,206 for the FPE group and €113,790 for the Non-FPE group. Of these, 83% were associated with long-term costs. Overall, the FPE group generated a cost reduction of €16,583 per patient in a lifetime horizon. Cost reductions are predicted to be greater when nursing/residential care cost are included, leading to a savings of €30,072 per patient.

In terms of health outcomes, the model estimates that achieving FPE lead to a QALY gain of 1.2 years (7.89 vs 6.69), while the number of independent people at 90 days is also projected to increase by 116 (662 vs 546) in this hypothetical cohort. However, there is an estimated increase in the total number of recurrent strokes in the FPE group due to patients living longer (283 vs 257).

The model suggests that achieving FPE lead to a NMB of €52,634 considering a WTP of €30,000/QALY gained. The NMB was expected to increase to €66,122 when nursing/residential care cost are considered. FPE provides greater net economic value demonstrating higher efficacy with lower costs from the payer perspective in a lifetime time horizon (Table 2). In the alternative scenario, similar results were observed, which may confirm the greater benefits that achieving FPE (between 32%-47% higher) may provide when all patients regardless their final mTICI are considered (QALY gain of 1.75 years and €21,910 cost reduction; when considering nursing/residential costs, a cost reduction of €44,289 and a NMB of €96,684) (Table 2).

Table 2. Summary of Base-case and Alternative scenario Results

	Base-case			**Alternative scenario**		
Costs	**FPE**	**Non-FPE**	**Incremen-tal**	**FPE**	**Non-FPE**	**Incremen-tal**
Treatment (€)	9,086	10,432	-1,346	9,086	10,432	-1,346

Adverse event costs (€)	269	582	-313	238	551	-314
Acute costs (€)	5,259	5,353	-94	5,250	5,387	-137
Long term care costs (€)	79,296	94,263	-14,968	78,039	98,469	-20,430
Long term care costs (With nursing/residential care cost) (€)	144,072	172,527	-28,456	141,678	184,487	-42,809
Recurrent stroke costs (€)	3,297	3,160	137	3,313	2,997	316
Total costs (€)	**97,206**	**113,790**	**-16,583**	**95,925**	**117,836**	**-21,910**
NMB (€)			52,634			74,306
Total costs (With nursing/residential care cost) (€)	**161,982**	**192,054**	**-30,072**	**159,565**	**203,854**	**-44,289**
NMB (With nursing/residential care cost) (€)			66,122			96,684
Total QALYs	7.89	6.69	1.2	7.96	6.21	1.75
Total life years	10.99	10.06	0.92	11.03	9.71	1.32

Sensitivity analysis

According to the DSA, in both scenarios (base-case and alternative), the key drivers of the analysis included long-term stroke care costs, starting age, health state utilities by mRS score, and relative risk of death. However, none of these key parameters changed the direction of the results; therefore, in all the simulations, the NMB remained positive (minimum value: €34,609; maximum value: €73,620), showing the results were robust to input parameters variations (Figure 2). In the PSA, FPE was estimated to be cost-neutral or cost-saving in 98.4%of the Monte Carlo simulations (Figure 3).

[Insert Figure 2]

[Insert Figure 3]

DISCUSSION

Clinical evidence suggests that achieving FPE after a single pass is associated with favourable outcomes after a MT procedure (6,7). Our study estimated the health gains from achieving FPE and examined the associated economic impact from the Spanish NHS perspective over a lifetime horizon.

Clinical outcomes, based on a sub-analysis from the STRATIS registry, showed that achieving mTICI 2c-3 reperfusion after a single pass leads to significantly better overall mRS distribution and functional independence (mRS 0-2). The difference in the proportion in mRS 0-2 between FPE and Non-FPE groups ranged between 11.5% to 16.3% depending on the cohort of patients (Figure 1). Similar findings have been described in literature (8). An analysis of North American Solitaire Acute Stroke Registry conducted by Zaidat et al. suggested that if patients achieved mTICI 3, the FPE lead to better clinical outcomes compared to the rest of the cohort that did not achieve FPE (61.3% vs 35.3%, p-value:<0.0001) (8).

The base-case results suggest that achieving FPE yields better health outcomes than Non-FPE group, providing an incremental QALY gain of 1.2 (in alternative scenario, QALY gain of 1.75), equivalent to 438 days in perfect health (657 days for alternative scenario). From the cost perspective, both scenarios suggest that the FPE group is associated with lower health care costs, leading to a cost-saving of €16,583 in the base-case scenario, €30,072 when considering nursing/residential healthcare costs, and -€21,910 to €44,289 in the alternative scenario) (Table 2). Cost savings in both scenarios were mainly driven by reductions in long-term costs associated with the management of functionally dependent patients. Furthermore, all results were tested by performing DSA and PSA which demonstrated that our results are robust. In

both scenarios and sub-scenarios, the Non-FPE group was associated with lower health benefits and higher health care costs.

A recently published study (21) estimated the short-term cost implications of FPE in several countries, including Spain. The authors estimated the procedural/hospitalization and annual care costs differences considering a 1-year time horizon. Similar to our work, the study showed lower procedural/hospitalization and annual care costs for patients that achieved FPE vs. Non-FPE across countries considered. Furthermore, our findings are compatible with other studies undertaken in the United States that have demonstrated that achieving TICI 3 lead to healthcare and societal cost savings relative to achieving TICI 2b for LVO (22,23).

Overall, the results of this study showed that raising the FPE rate will not only increase the quality of life for patients, but also decrease the overall health care costs. Achieving FPE can potentially be one of the primary goals in the treatment of patients with ischemic stroke due to LVO from both a clinical and economic perspective. Because this analysis was performed from the Spanish NHS perspective, only the direct costs are considered. There could be larger savings associated with achieving FPE if indirect costs, such as informal care and productivity losses, were included.

To our knowledge, this is one of the first studies that aim to evaluate the lifetime health and cost implications of achieving FPE in AIS patients in Spain from the NHS perspective. Among the strengths of this study are the Markov structure (allows to better reflect the patient pathway in terms of lifetime costs and benefits) and the inclusion of comprehensive diagnostics and treatments costs, main adverse events management, and recurrent strokes, to account for all health outcomes and associated costs after a stroke.

This study has some limitations. First, clinical efficacy and patient characteristics were based on the STRATIS registry, which included centers outside Spain. Furthermore, the STRATIS registry is based on specific stent retrievers and might not be applicable to other types of devices with different safety and efficacy profile. Also, the average age for a stroke onset in Spain might be higher than our assumption for all patients (68 years), which could potentially lead to an overestimation of health outcomes. However, age was included in the DSA, varied to an upper limit of 75 years, and this did not lead to dramatic changes in the results as the NMB remained positive in all scenarios. Third, patients were assumed to remain in a given mRS score until they experienced a recurrent stroke or death. Other factors that may have an effect on mRS scores, such as comorbidities, were not included. However, this aspect should affect both patient cohorts equally. Acute and long-term costs were obtained from the original cost-effectiveness model and the same limitations for costs would apply. Finally, resource consumption was based on a panel of experts' consensus and clinical practice and subject to heterogeneity between centres. However, these assumptions were tested in the DSA and PSA and did not alter the overall results.

CONCLUSION

Achieving FPE after MT can lead to important health care cost-saving and better functional clinical outcomes per patient compared to not achieving FPE. Costs saving to the Spanish NHS ranged from -€16,583 to -€44,289 depending on the patient cohort and long-term costs. Increasing FPE rates will lead to greater cost savings to the health care system.

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Contributors: EGD, CRP, AFP, RMM, JOQ, JZ, AT and MMG: contributed in the design, data collection, analysis, interpretation and drafting, reviewing, and revising the manuscript. NHMK, OOZ and DSL: reviewing and revising the manuscript

Patient consent for publication: Not required.

Data Sharing Statement: All relevant model inputs used in this study are included in the article and supplement.

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Figure Legends

Figure 1. mRS outcomes at 90 days Base case and Alternative Scenario.

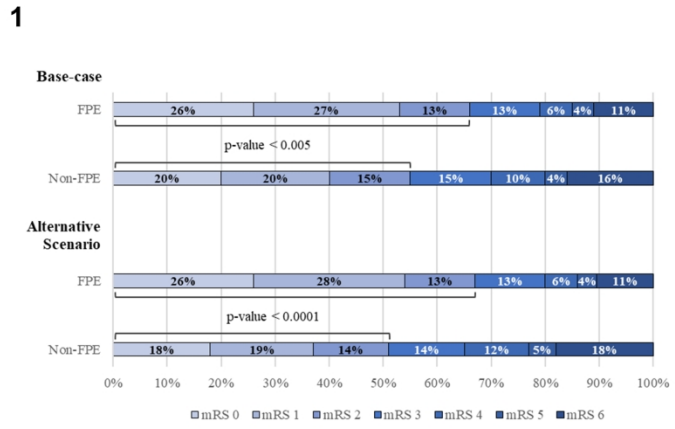
Acronyms: FPE (First Pass Effect); mRS (modified Rankin Score);

Figure 2. Tornado diagram of deterministic sensitivity analysis

Acronyms: FPE (First Pass Effect); mRS (modified Rankin Score); RR (Relative Risk)

Figure 3. Probabilistic sensitivity analysis

Acronyms: QALYs (Quality-Adjusted Life Years).



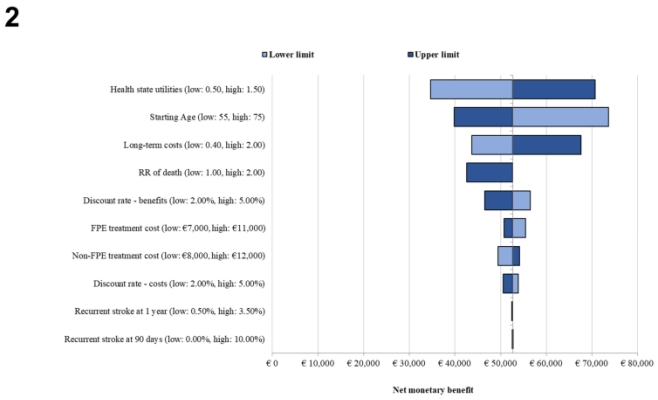


Figure 1 - mRS outcomes at 90 days Base case and Alternative Scenario. Acronyms: FPE (First Pass Effect); mRS (modified Rankin Score). Figure 2 - Tornado diagram of deterministic sensitivity analysis. Acronyms: FPE (First Pass Effect); mRS (modified Rankin Score); RR (Relative Risk)

190x275mm (300 x 300 DPI)

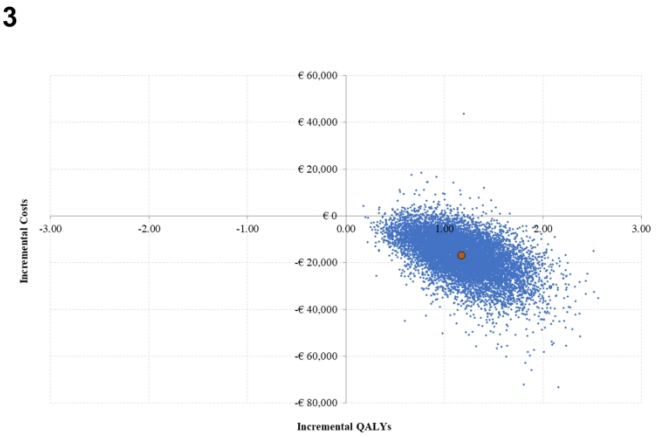


Figure 3 - Probabilistic sensitivity analysis. Acronyms: QALYs (Quality-Adjusted Life Years).

190x275mm (300 x 300 DPI)

Economic analysis of the first pass effect in mechanical thrombectomy for acute ischemic stroke treatment in Spain.

Supplementary Material

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Table A1. Relative risk of death by mRS [1]

mRS score	RR
mRS 0	1.00
mRS 1	1.00
mRS 2	1.12
mRS 3	1.66
mRS 4	1.92
mRS 5	2.57

Table A2. Lifetable Spain by age and gender [2]

Other-cause mortality		
Age	**Male**	**Female**
0	0.276%	0.245%
1	0.023%	0.018%
2	0.013%	0.008%
3	0.012%	0.009%
4	0.014%	0.007%
5	0.010%	0.009%
6	0.007%	0.006%
7	0.007%	0.005%
8	0.009%	0.007%
9	0.007%	0.004%
10	0.007%	0.006%
11	0.008%	0.007%
12	0.007%	0.007%
13	0.010%	0.005%
14	0.008%	0.013%
15	0.013%	0.011%
16	0.021%	0.011%
17	0.016%	0.015%
18	0.030%	0.014%
19	0.026%	0.010%
20	0.029%	0.014%
21	0.034%	0.015%
22	0.030%	0.014%
23	0.037%	0.014%
24	0.039%	0.019%
25	0.032%	0.019%
26	0.048%	0.015%

27	0.036%	0.014%
28	0.049%	0.018%
29	0.055%	0.018%
30	0.046%	0.028%
31	0.054%	0.022%
32	0.048%	0.022%
33	0.052%	0.025%
34	0.062%	0.031%
35	0.062%	0.034%
36	0.066%	0.033%
37	0.065%	0.036%
38	0.071%	0.042%
39	0.082%	0.044%
40	0.091%	0.052%
41	0.098%	0.059%
42	0.107%	0.059%
43	0.123%	0.073%
44	0.120%	0.069%
45	0.143%	0.087%
46	0.169%	0.095%
47	0.191%	0.112%
48	0.228%	0.110%
49	0.244%	0.143%
50	0.289%	0.149%
51	0.325%	0.162%
52	0.349%	0.173%
53	0.388%	0.211%
54	0.473%	0.220%
55	0.517%	0.233%
56	0.557%	0.259%
57	0.601%	0.286%
58	0.675%	0.312%
59	0.720%	0.339%
60	0.803%	0.364%
61	0.895%	0.384%
62	0.977%	0.420%
63	1.055%	0.451%
64	1.116%	0.496%
65	1.219%	0.504%
66	1.318%	0.574%
67	1.436%	0.616%
68	1.514%	0.620%

69	1.700%	0.720%
70	1.911%	0.787%
71	1.990%	0.849%
72	2.215%	0.937%
73	2.370%	1.051%
74	2.627%	1.233%
75	2.872%	1.403%
76	3.074%	1.570%
77	3.492%	1.763%
78	4.139%	2.142%
79	4.500%	2.474%
80	5.153%	2.928%
81	5.708%	3.368%
82	6.436%	3.838%
83	7.209%	4.440%
84	8.410%	5.257%
85	9.184%	6.197%
86	10.539%	7.184%
87	11.846%	8.422%
88	13.304%	9.728%
89	15.057%	11.340%
90	16.914%	13.272%
91	19.683%	14.947%
92	20.636%	16.507%
93	23.300%	18.967%
94	25.526%	21.541%
95	27.536%	23.666%
96	29.487%	26.675%
97	31.265%	28.241%
98	32.711%	29.794%
99	26.429%	30.496%
100	48.238%	46.382%

Table A3. Recurrent Stroke Rates [3]

Year	Recurrent Stroke Rate
Year 1	4.91%
Year 2 onwards	2.01%

Table A4. Health States Utilities [4]

mRS	Utility
mRS 0	0.936
mRS 1	0.817
mRS 2	0.681
mRS 3	0.558
mRS 4	0.265
mRS 5	-0.054
mRS 6	0

Table A5. Unit costs, consumption and total management costs for each group of patients [5] [6]

AIS diagnosis + IV-tPA (tPA 30% of patients)			
Item	**Unit cost (€)**	**Units**	**Total cost (€)**
Neurologist	36.19	1.0	36.19
Neuroradiologist	36.19	0.5	18.09
Resident Doctor	12.56	1.0	12.56
Nurse 1	22.01	0.5	11.01
Nurse 2	22.01	0.5	11.01
Technician	17.54	0.5	8.77
Cranial CT scan	84.83	1.0	84.83
Blood test	46.10	1.0	46.10
Electrocardiogram	40.26	1.0	40.26
Chest Radiograph	26.58	0.5	13.29
Computerized tomography angiography	279.25	1.0	279.25
Perfusion computerized tomography	252.17	0.5	126.08
Nursing Assistant 1	13.07	0.5	4.71
Orderly	13.07	0.5	6.53
Alteplase (0,9 mg/kg; average patient weight 75 kg), (30% of the patients)	9.85	67.5	199.67
MRI (0.5% of the patients)	204.48	0.05	3.07
Costs group "FIRST PASS"			
Stent retriever	3.388	1.0	3.388
Intracranial catheter	2.178	1.0	2.178
Ballon guide catheter/ Long Sheath	786.5	1.0	786,5
Guide/Microguide (0.35/0.12/0.14)	484	1.0	484
Microcatheter	605	1.0	605
Introducer	15.73	1.0	15.73
Procedure pack + gloves	32.05	1.0	32.05
Vascular closure device	187.67	1.0	187.67
Diagnosis catheter + contrast	50.05	1.0	50.05

PTA balloon catheter	250.23	0.3	75.07
Carotid stent	1,376.25	0.15	206.44
Anesthetist	36.19	3.0	108.56
Neurologist	36.19	0.2	7.24
Neuroradiologist	36.19	3.0	108.56
Orderly	13.07	0.5	6.53
Nurse	22.01	6.0	132.07
Cranial computerized tomography scan	84.83	1.0	84.83
Costs group "Non-FIRST PASS"			
Stent retriever	3,388	1.20	4,065.60
Intracranial catheter	2,178	1.20	2,613.60
Balloon guide catheter/ Long Sheath	786.5	1.00	786.50
Guide/Microguide (0.35/0.12/0.14)	484	1.20	580.80
Microcatheter	605	1.10	665.50
Introducer	15.73	1.00	15.73
Procedure pack + gloves	32.05	1.00	32.05
Vascular closure device	187.67	1.00	187.67
Diagnosis catheter + contrast	50.05	1.00	48,40
PTA balloon catheter	250.23	0.30	75.07
Carotid stent	1,376.25	0.15	206.44
Anesthetist	36.19	4.00	144.75
Neurologist	36.19	0.20	7.24
Neuroradiologist	36.19	4.00	144.75
Orderly	13.07	0.5	6.53
Nurse	22.01	8.00	176.09
Cranial computerized tomography scan	84.83	1.00	84.83

Table A6 – Subject Demographics and Baseline Characteristics (Base-case Population) [7]

Characteristic	FPE (N=304)	Non FPE (N=350)	P value (FPE vs. non FPE)
Age (years)	69.9±14.93(304) 72.0(61-80)	66.7±14.70(350) 68.0(58-79)	0.7771
Sex (Male)	162/304(53.3%)	189/350(54.0%)	0.8558
Pre-stroke mRS			0.0152
0	220/304(72.4%)	280/350(80.0%)	
1	72/304(23.7%)	63/350(18.0%)	
2*	12/304(3.9%)	7/350(2.0%)	
Initial Qualifying NIHSS Score (Baseline NIHSS)	17.0±5.41(304) 17.0(13-21)	17.3±5.54(350) 18.0(12-21)	0.6769
Total ASPECTS Score	8.3±1.53(266) 9.0(8-9)	8.1±1.59(303) 8.0(8-9)	0.4737
IV tPA administered	181/304(59.5%)	237/350(67.7%)	0.0299
IA-tPA used	29/303(9.6%)	63/348(18.1%)	0.0018
General Anesthesia Used (Site-Reported)	78/303(25.7%)	109/348(31.3%)	0.1166
Stroke onset to puncture (min)	226.6±99.90(301) 215.0(150-295)	217.4±99.33(349) 194.0(143-278)	0.9172

Summary statistics: Mean±SD(n), Median (IQR) for continuous and n/N (%) for categorical variables.

*Patients with Pre-mRS of 2 are enrolled under Rev B protocol.

Each P-value was based on T test (2-sided) for the mean difference and Z test (2-sided) for the proportion difference between FPE and non FPE;mRS scores between FPE and Non-FPE are compared using using Mantel-Haenszel Chi-square test.

Table A7 – Subject Demographics and Baseline Characteristics (Alternative scenario Population) [7]

Characteristic	FPE (N=317)	Non FPE (N=431)	P value (FPE vs. non FPE)
Age (years)	69.7±14.85(317) 72.0(61-80)	67.1±14.61(431) 68.0(58-79)	0.7459
Sex (Male)	170/317(53.6%)	225/431(52.2%)	0.6999
Pre-stroke mRS			0.0380
0	230/317(72.6%)	340/431(78.9%)	
1	75/317(23.7%)	81/431(18.8%)	
2*	12/317(3.8%)	10/431(2.3%)	
Initial Qualifying NIHSS Score (Baseline NIHSS)	17.1±5.41(317) 17.0(13-21)	17.3±5.54(431) 18.0(12-21)	0.6550
Total ASPECTS Score	8.3±1.51(275) 9.0(8-9)	8.1±1.65(378) 8.0(7-9)	0.1184
IV tPA administered	193/317(60.9%)	285/431(66.1%)	0.1402
IA-tPA used	31/316(9.8%)	79/428(18.5%)	0.0010
General Anesthesia Used (Site-Reported)	80/316(25.3%)	138/428(32.2%)	0.0402
Stroke onset to puncture (min)	227.2±100.86(314) 213.5(150-295)	222.9±101.11(428) 199.5(146-290)	0.9660

Summary statistics: Mean±SD(n), Median (IQR) for continuous and n/N (%) for categorical variables.

*Patients with Pre-mRS of 2 are enrolled under Rev B protocol.

Each P-value was based on T test (2-sided) for the mean difference and Z test (2-sided) for the proportion difference between FPE and non FPE;mRS scores between FPE and Non-FPE are compared using using Mantel-Haenszel Chi-square test.

Table A8 – Medical and Neurological History (Base-case Population) [7]

	FPE (N=304)	Non FPE (N=350)	P value (FPE vs. non FPE)
Atrial flutter/Atrial fibrillation	128/304(42.1%)	120/350(34.3%)	0.0398
Systemic Hypertension	217/304(71.4%)	262/350(74.9%)	0.3166
Diabetes mellitus	91/304(29.9%)	93/350(26.6%)	0.3401
Myocardial disease/Coronary artery disease	95/304(31.3%)	85/350(24.3%)	0.0467
Hyperlipidemia	129/304(42.4%)	155/350(44.3%)	0.6337
Peripheral artery disease	13/304(4.3%)	13/350(3.7%)	0.7137
Carotid artery disease	33/304(10.9%)	17/350(4.9%)	0.0040
Current or former tobacco use	137/304(45.1%)	162/350(46.3%)	0.7548
Neurological history			
Previous ischemic stroke	43/304(14.1%)	34/350(9.7%)	0.0795
Previous hemorrhagic stroke	3/304(1.0%)	3/350(0.9%)	0.8622
Previous TIA	20/304(6.6%)	17/350(4.9%)	0.3418
Brain aneurysm	3/304(1.0%)	1/350(0.3%)	0.2514

Summary Statistics for categorical: n/N (%)

Each P-value was based on Z test (2-sided) for the proportion difference between FPE and non-FPE

Table A9 – Medical and Neurological History (Alternative scenario Population) [7]

	FPE (N=317)	Non FPE (N=431)	P value (FPE vs. non FPE)
Atrial flutter/Atrial fibrillation	134/317(42.3%)	152/431(35.3%)	0.0514
Systemic Hypertension	223/317(70.3%)	327/431(75.9%)	0.0907
Diabetes mellitus	91/317(28.7%)	111/431(25.8%)	0.3688
Myocardial disease/Coronary artery disease	96/317(30.3%)	112/431(26.0%)	0.1948
Hyperlipidemia	132/317(41.6%)	192/431(44.5%)	0.4278
Peripheral artery disease	13/317(4.1%)	16/431(3.7%)	0.7856
Carotid artery disease	35/317(11.0%)	27/431(6.3%)	0.0192
Current or former tobacco use	143/317(45.1%)	202/431(46.9%)	0.6338
Neurological history			
Previous ischemic stroke	46/317(14.5%)	43/431(10.0%)	0.0584
Previous hemorrhagic stroke	3/317(0.9%)	4/431(0.9%)	0.9795
Previous TIA	20/317(6.3%)	22/431(5.1%)	0.4794
Brain aneurysm	4/317(1.3%)	3/431(0.7%)	0.4271

Summary Statistics for categorical: n/N (%)

Each P-value was based on Z test (2-sided) for the proportion difference between FPE and non-FPE

Table A10. Adverse events Base-Case and alternative scenario

Patient group **Base case**	**symptomatic intracranial hemorrhage***	**malignant cerebral edema**
FPE	0.7%	1%
Non-FPE	2.3%	1.4%
P-values are obtained from Fisher's exact test	0.1154	0.7303
Patient group **Alternative Scenario**	**symptomatic intracranial hemorrhage**	**malignant cerebral edema**
FPE	0.6%	0.9%
Non-FPE	2.1%	1.4%
P-values are obtained from Fisher's exact test.	0.1297	0.7403
*sICH is defined as any PH1, PH2, RIH, IVH or SAH per imaging core lab and associated with ≥ 4 points worsening on the NIHSS scale within 24 hours.		

References:

1. Slot KB, Berge E, Sandercock P, et al. Causes of death by level of dependency at 6 months after ischaemic stroke in 3 large cohorts. Stroke 2009; 40: 1585–1589.
2. Instituto Nacional de Estadıstica. 2018 Mortality tables of Spanish population. National results. In: INEbase. [Internet]. 2018 [cited 2020 Oct 10]. Available from: www.ine.es
3. Mohan KM, Wolfe CDA, Rudd AG, Heuschmann PU, Kolominsky-Rabas PL, Grieve AP. Risk and cumulative risk of stroke recurrence: A systematic review and meta-analysis. Stroke. 2011;42(5):1489–94. E
4. Rivero-Arias O, Ouellet M, Gray A, Wolstenholme J, Rothwell PM, Luengo-Fernandez R. Mapping the modified rankin scale (mRS) measurement into the generic EuroQol (EQ-5D) health outcome. Med Decis Mak. 2010;30(3):341–54.
5. de Andrés-Nogales F, Álvarez M, de Miquel MÁ, Segura T, Gil A, Cardona P, et al. Cost-effectiveness of mechanical thrombectomy using stent retriever after intravenous tissue plasminogen activator compared with intravenous tissue plasminogen activator alone in the treatment of acute ischaemic stroke due to large vessel occlusion in Spa. Eur Stroke J. 2017;2(3):272–84.
6. Expert opinion
7. Mueller-Kronast NH, Zaidat OO, Froehler MT, Jahan R, et al. Systematic Evaluation of Patients Treated With Neurothrombectomy Devices for Acute Ischemic Stroke: Primary Results of the STRATIS Registry. Stroke. 2017;48(10):2760–8.

CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force*, provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Lines 1-2
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Lines 44-71
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	Lines 95-115 Lines 117-119
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Lines 147-152
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Line 127
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Line 127 Lines 180-182
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Lines 126-129
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Line 129
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Lines 191-192
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Lines 199-202
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	NA

	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	NA
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	NA
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	NA
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Lines 182-190
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Lines 190-191
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Lines 134-144
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Lines 134-144
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Lines 143-144 Lines 161-164 Lines 204-211
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Table 1 Tables A1 - A9
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Table 2
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	NA

		of methodological assumptions (such as discount rate, study perspective).	NA
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Lines 259-265
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Table 2
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Lines 287-297 Lines 322-336
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Lines 351-352
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Lines 355-360

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

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Economic impact of the first pass effect in mechanical thrombectomy for acute ischemic stroke treatment in Spain: a cost-effectiveness analysis from the national health system perspective.

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Economic impact of the first pass effect in mechanical thrombectomy for acute ischemic stroke treatment in Spain: a cost-effectiveness analysis from the national health system perspective.

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Abstract

Objective: The mechanical thrombectomy (MT) benefit is related to the degree of reperfusion achieved. First Pass Effect (FPE) is defined as complete/near revascularization of the large vessel occlusion (modified Thrombolysis in Cerebral Infarction (mTICI) 2c-3) after a single device pass. This study assessed the health benefit and economic impact of achieving FPE for acute ischemic stroke (AIS) patients from the Spanish National Health System (NHS) perspective.

Design: A lifetime Markov model was used to estimate incremental costs and health outcomes (measured in quality-adjusted life-years [QALY]) of patients that achieve FPE. A sub-analysis of the STRATIS registry was performed to obtain clinical outcomes. The base-case included all patients that achieved at least a final mTICI≥2b, while the alternative scenario included all patients regardless of their final mTICI (0-3). Treatment costs were updated to reflect current practice based on expert panel consensus, while other acute and long-term costs were obtained from a previous cost-effectiveness analysis of MT performed in Spain. Sensitivity analyses were performed to assess the model's robustness.

Setting: Spanish healthcare perspective.

Participants: AIS patients in Spain.

Interventions: FPE following MT.

Outcome measures: The model estimated QALYs, lifetime costs and net monetary benefit (NMB) for the FPE and non-FPE group, depending on the inclusion of reperfusion groups and formal care costs.

Results: STRATIS sub-analysis estimated significantly better clinical outcomes at 90-days for the FPE group in all scenarios. In the base-case, the model estimated lifetime cost-saving per patient of €16,583 and an incremental QALY gain of 1.2 years of perfect health for the FPE

group. Cost-savings and QALY gains were greater in the alternative scenario (-€44,289; 1.75). In all scenarios, cost-savings were driven by the long-term cost reduction.

Conclusion: Achieving FPE after MT can lead to better health outcomes per AIS patient. and important cost-savings for the Spanish NHS.

Article Summary

Strengths and limitations of this study

- A Markov model estimated the lifetime health and cost implications of achieving FPE in AIS patients treated with Mechanical Thrombectomy in Spain from the NHS perspective.
- The model allows to quantify the benefits of aiming mechanical thrombectomy techniques that may increase the first pass effect success rates.
- A limitation of this study is that clinical efficacy and patient characteristics were based on the STRATIS registry, which included centers outside Spain.
- Another limitation is that some model parameters, such as acute and long-term costs have been derived from literature, which have been validated by clinical experts.

INTRODUCTION

The annual number of strokes in the European Union is forecasted to increase by 34% in 2035, mainly due to its aging population. With improving survival rates after stroke, almost 1 million more people will be living with a stroke as a chronic condition, rising from 3.7 million in 2015 to 4.6 million in 2035 (1). It is estimated that the incidence and prevalence of strokes will increase by 35% and 31% respectively in Spain by 2035 (2), which will inevitably raise the associated economic burden.

Mechanical thrombectomy (MT) is the most effective reperfusion treatment used in acute ischemic stroke (AIS) management in patients with large vessel occlusion (LVO) (3,4). Its cost-effectiveness has already been demonstrated in Spain; improving functional outcomes is associated with a higher quality of life and reduced health costs, leading to €44,378 in savings per patient compared to thrombolysis with intravenous tissue-type plasminogen activator (IV-tPA) alone (5).

Clinical evidence suggests that the number of passes during a MT inversely correlates with the functional outcome of the procedure (6,7). Achieving complete/near revascularization of the LVO (modified Thrombolysis in Cerebral Infarction [mTICI] 2c-3) after a single pass with MT, known as first pass effect (FPE), is associated with significant improvements in clinical outcomes and can be considered an independent predictor of good functional outcomes (8). Recent studies have begun to try to identify factors or predictors of first pass effect which may impact the choice of thrombectomy device and technique in the future (8–11).

The objective of this study is to assess the health outcome benefits and economic impact of achieving FPE for the AIS patients from the National Health System (NHS) perspective in Spain.

METHODS

Model structure

A previously published cost-effectiveness model comparing MT + IV-tPA with IV-tPA alone in a Spanish NHS setting was modified to reflect only patients that received MT treatment which afterwards were stratified to reflect those who achieved FPE and those who didn't (Non-FPE) (5), and allowed to estimate lifetime health and costs outcomes of the two patient groups. As in the previous modelling, this analysis is also over the patient's lifetime and from the Spanish NHS perspective. The model was developed using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA).

The model had a two-phase structure, consisting of an acute-subacute phase from stroke onset to 90 days, and a rest-of-life phase 91 days after stroke to the end of patient's life. In the acute-subacute phase, patients enter the model once reperfusion status (FPE vs Non-FPE) has been determined, and then are assigned to one of the seven mutually exclusive health states based on Modified Ranking Scale (mRS; 0-no symptoms, 6-death) to reflect several degrees of disability at 90 days. Afterwards, patients enter a Markov structure, from 91 days after the stroke to the end of the patients' life. In this phase, patients could remain in the same health state or transition to different states during each annual cycle until the end of life, depending

on the occurrence of a recurrent stroke or death from other causes (age-gender specific mortality). A half-cycle correction was used to account for transitions occurring in the middle of a cycle.

Patient population

The model simulates a hypothetical cohort of 1,000 patients with clinic-demographic characteristics based on the STRATIS registry (Systematic Evaluation of Patients Treated With Neurothrombectomy Devices for Acute Ischemic Stroke) (12). STRATIS registry patients were classified into 2 groups: patients with a final mTICI ≥2b (used for the base case analysis), and patients with final mTICI (0-3) (used for the alternative scenario). Afterwards, patients in both groups were stratified into FPE and non-FPE groups.

Clinical data

Clinical data was obtained from a sub-analysis of the STRATIS registry (12) in which FPE and Non-FPE groups were compared. Moreover, it was considered that patients were at risk of experiencing adverse events (symptomatic intracranial hemorrhage and malignant cerebral edema) during the acute-subacute phase, therefore adverse events data was also obtained from STRATIS registry sub-analysis.

Categorical variables were compared using $\chi 2$ (Chi-square) test and Mantel-Haenszel Chi-square test when appropriate. Proportion differences were compared by z-test both one-sided and two-sided tests are performed (considering 5% and 2.5% significance level respectively). All statistical analyses were performed using SAS version 9.4.

Background age-gender related mortality was obtained from the latest available Life Table in Spain (data from 2018) (13) and relative risks of death by mRS score were used to adjust age-gender-related mortality (14) to account for the increased risks observed among stroke survivors (Supplementary Material Table A1 & A2). Recurrence stroke rates were obtained from Mohan et al. (15) (Supplementary Material (Table A3).

Quality of life

Health outcomes were measured using quality-adjusted life years (QALY), a measure that weights life-years gained with an intervention by its utility value. Utilities assigned to health states can take values from 0 (death) to 1 (optimal health) and negative values (state worse than death). Utilities by mRS score were obtained from Rivero-Arias et al. 2010 (16), with values ranging from 0.93 (mRS 0) to -0.54 (mRS 5) (Supplementary Material (Table A4).

Costs

The study considered the Spanish NHS perspective, consequently, only direct medical costs were considered, including treatment and adverse events management costs, acute and long-term care costs. Treatment costs were updated to reflect the costs for each patient group (FPE vs Non-FPE) and were kept in line with the new treatment approaches according to local practice based on a panel of experts' consensus. Treatment costs in both groups FPE and Non-FPE included the costs of AIS diagnosis, and adjunctive IV-tPA in 30% of the cases according to local practice (Table A5, Supplementary Material).

Adverse events, acute and long-term costs by mRS score were kept consistent with the previous model (5). For each scenario, a second analysis was performed to include formal care costs such as nursing/residential costs. All costs are presented in Euros and were inflated to reflect

Euros in 2020 (Table 1). Costs and health outcomes were discounted at an annual discount rate of 3% consistent with the relevant health technology assessment guidelines for Spain (17).

Table 1. Adjusted Acute and long-term costs (Euros 2020)

mRS	Acute costs	Annual long-term cost	
	Total Acute care cost (€)	**Total Long-term healthcare cost (without nursing and residential care cost) (€)**	**Total including nursing and residential care cost (€)**
mRS 0	4,718	1,340	2,767
mRS 1	5,242	1,489	3,074
mRS 2	5,766	1,638	3,382
mRS 3	6,468	23,250	33,061
mRS 4	7,187	25,833	53,339
mRS 5	7,906	28,417	67,400
mRS 6	4,046		

Note: Table adapted from De Andrés-Nogales et al., 2017 (6)

Economic model outcomes and sensitivity analysis

The model estimates the lifetime total costs and QALYs for each patient group. To quantify the net economic value of FPE, the net monetary benefit (NMB) was calculated, considering a willingness-to-pay (WTP) threshold of €30,000/QALY, (NMB=(Incremental QALYs×WTP)-Incremental Costs) (18,19).

Deterministic Sensitivity Analysis (DSA) and Probabilistic Sensitivity Analysis (PSA) were conducted to evaluate results' robustness (20). DSA assigns a one-way variation to input parameters including discount rates, mRS at 90 days, age, health states utilities, recurrent stroke rates, relative risk of death, and all costs (treatment, acute and long-term costs). In PSA, 10,000 Monte Carlo simulations were run after assigning a probability distribution to all key

parameters simultaneously (mRS scores at 90 days (Dirichlet), mortality relative risks (Lognormal), starting age (Normal), utilities (Beta) and costs (Gamma)), to account for the general uncertainty around model inputs (5).

Patient and public involvement

This study was conducted without patient and public involvement. Therefore, patients were not involved in the study design, reporting or interpretation of the findings. This study included a post-hoc analysis of an existing study, therefore institutional review board approval was not obtained for this analysis. Moreover, no research approval was required for model input parameters that were obtained from literature or based on panel of experts consensus.

RESULTS

Based on STRATIS sub-analysis, the mean age of stroke considered in the model was 68 years. Both groups have similar characteristics at baseline. Descriptive statistics on the FPE and Non-FPE groups are reported in Supplementary Material, Tables A6-A7-A8-A9.

Our results suggest that the FPE group had significantly better clinical outcomes at 90 days after stroke compared to the Non-FPE group in the base-case scenario (mRS 0-2: 66.2% vs 54.6%, p-value<0.005). Similar results in the alternative scenario were observed (mRS 0-2: 66.9% vs 50.6%, p-value<0.0001) (Figure 1). Adverse events results across scenario populations are presented in the Supplementary Material (Table A10).

[Insert Figure 1]

In the base-case scenario, the model estimates an average lifetime cost per patient equal to €97,206 for the FPE group and €113,790 for the Non-FPE group. Of these, 83% were associated with long-term costs. Overall, the FPE group generated a cost reduction of €16,583 per patient in a lifetime horizon. Cost reductions are predicted to be greater when nursing/residential care cost are included, leading to a savings of €30,072 per patient.

In terms of health outcomes, the model estimates that achieving FPE lead to a QALY gain of 1.2 years (7.89 vs 6.69), while the number of independent people at 90 days is also projected to increase by 116 (662 vs 546) in this hypothetical cohort. However, there is an estimated increase in the total number of recurrent strokes in the FPE group due to patients living longer (283 vs 257).

The model suggests that achieving FPE lead to a NMB of €52,634 considering a WTP of €30,000/QALY gained. The NMB was expected to increase to €66,122 when nursing/residential care cost are considered. FPE provides greater net economic value demonstrating higher efficacy with lower costs from the payer perspective in a lifetime time horizon (Table 2). In the alternative scenario, similar results were observed, which may confirm the greater benefits that achieving FPE (between 32%-47% higher) may provide when all patients regardless their final mTICI are considered (QALY gain of 1.75 years and €21,910 cost reduction; when considering nursing/residential costs, a cost reduction of €44,289 and a NMB of €96,684) (Table 2).

Table 2. Summary of Base-case and Alternative scenario Results

	Base-case			Alternative scenario		
Costs	**FPE**	**Non-FPE**	**Incremen-tal**	**FPE**	**Non-FPE**	**Incremen-tal**
Treatment (€)	9,086	10,432	-1,346	9,086	10,432	-1,346
Adverse event costs (€)	269	582	-313	238	551	-314
Acute costs (€)	5,259	5,353	-94	5,250	5,387	-137
Long term care costs (€)	79,296	94,263	-14,968	78,039	98,469	-20,430
Long term care costs (With nursing/residential care cost) (€)	144,072	172,527	-28,456	141,678	184,487	-42,809
Recurrent stroke costs (€)	3,297	3,160	137	3,313	2,997	316
Total costs (€)	**97,206**	**113,790**	**-16,583**	**95,925**	**117,836**	**-21,910**
NMB (€)			52,634			74,306
Total costs (With nursing/residential care cost) (€)	**161,982**	**192,054**	**-30,072**	**159,565**	**203,854**	**-44,289**
NMB (With nursing/residential care cost) (€)			66,122			96,684
Total QALYs	7.89	6.69	1.2	7.96	6.21	1.75
Total life years	10.99	10.06	0.92	11.03	9.71	1.32

Sensitivity analysis

According to the DSA, in both scenarios (base-case and alternative), the key drivers of the analysis included long-term stroke care costs, starting age, health state utilities by mRS score, and relative risk of death. However, none of these key parameters changed the direction of the results; therefore, in all the simulations, the NMB remained positive (minimum value: €28,884; maximum value: €73,620), showing the results were robust to input parameters variations (Figure 2). In the PSA, FPE was estimated to be cost-neutral or cost-saving in 98.4%of the Monte Carlo simulations (Figure 3).

[Insert Figure 2]

272 **[Insert Figure 3]**

273

274

DISCUSSION

Clinical evidence suggests that achieving FPE after a single pass is associated with favourable outcomes after a MT procedure (6,7). Our study estimated the health gains from achieving FPE and examined the associated economic impact from the Spanish NHS perspective over a lifetime horizon.

Clinical outcomes, based on a sub-analysis from the STRATIS registry, showed that achieving mTICI 2c-3 reperfusion after a single pass leads to significantly better overall mRS distribution and functional independence (mRS 0-2). The difference in the proportion in mRS 0-2 between FPE and Non-FPE groups ranged between 11.5% to 16.3% depending on the cohort of patients (Figure 1). Similar findings have been described in literature (8)(21)(22). An analysis of North American Solitaire Acute Stroke Registry conducted by Zaidat et al. suggested that if patients achieved mTICI 3, the FPE lead to better clinical outcomes compared to the rest of the cohort that did not achieve FPE (61.3% vs 35.3%, p-value:<0.0001) (8). The meta-analysis by Abbasi et al. reported on the association between FPE and clinical outcomes finding higher rates of functional independence for FPE compared to Non-FPE (56% vs 41%, p-value: <0.01) and lower mortality (17% vs 25%, p-value: <0.01) (21). Furthermore, a recent meta-analysis that conducted a per-pass analysis of recanalization and health outcomes in thrombectomy (22) suggests that the likelihood of functional independence in patients with final successful recanalization decreased after each pass. On the first pass, 55% of patients achieved mRS 0-2 (p-value: 0.033), while rates progressive declined after each subsequent pass, dropping to 26% for patients who required 5 or more passes for successful recanalization. The results of our analysis also confirm improved health outcomes from achieving FPE and are therefore coherent with existing literature.

The base-case results suggest that achieving FPE yields better health outcomes than Non-FPE group, providing an incremental QALY gain of 1.2, equivalent to 438 days in perfect health. From the cost perspective, the FPE group is associated with lower health care costs, leading to a cost-saving of €16,583 and €30,072 when considering nursing/residential healthcare costs (Table 2). QALYs and cost-savings resulted to be greater in the alternative scenario: the FPE group lead to 1.75 additional QALYs per patient (or 657 days in full health) and €21,910 in savings (€44,289 when considering nursing/residential healthcare costs). The greater results observed in the alternative scenario can be explained by a slight increase in good functional outcomes in the FPE group, accompanied by a decrease in the mRS 0-2 in the non-FPE group, which contributed to an even larger incremental difference between FPE and non-FPE outcomes in this scenario.

Cost savings in both scenarios were mainly driven by reductions in long-term costs associated with the management of functionally dependent patients. Furthermore, all results were tested by performing DSA and PSA which demonstrated that our results are robust. In both scenarios and sub-scenarios, the Non-FPE group was associated with lower health benefits and higher health care costs.

Improved health outcomes are generally associated with economic benefits. Even though there is less literature available on cost-implications from FPE, a recently published study (23) estimated the short-term cost implications of FPE in several countries, including Spain. The authors estimated the procedural/hospitalization and annual care costs differences considering a 1-year time horizon. Similar to our work, the study showed lower procedural/hospitalization and annual care costs for patients that achieved FPE vs. Non-FPE across countries considered. Furthermore, our findings are compatible with other studies undertaken in the United States

that have demonstrated that achieving TICI 3 lead to healthcare and societal cost savings relative to achieving TICI 2b for LVO (24,25).

Overall, the results of this study showed that raising the FPE rate will not only increase the quality of life for patients, but also decrease the overall health care costs. Achieving FPE can potentially be one of the primary goals in the treatment of patients with ischemic stroke due to LVO from both a clinical and economic perspective. Because this analysis was performed from the Spanish NHS perspective, only the direct costs are considered. There could be larger savings associated with achieving FPE if indirect costs, such as informal care and productivity losses, were included.

To our knowledge, this is one of the first studies that aim to evaluate the lifetime health and cost implications of achieving FPE in AIS patients in Spain from the NHS perspective. Among the strengths of this study are the Markov structure (allows to better reflect the patient pathway in terms of lifetime costs and benefits) and the inclusion of comprehensive diagnostics and treatments costs, main adverse events management, and recurrent strokes, to account for all health outcomes and associated costs after a stroke.

This study has some limitations. First, clinical efficacy and patient characteristics were based on the STRATIS registry, which included centers outside Spain. Moreover, the study's reliance on observational data may limit the result’s interpretation due to the potential effect that unmeasured confounders (e.g., quality of stroke care, procedural technique) could have on the mRS score variation between groups. Furthermore, the STRATIS registry is based on specific stent retrievers and might not be applicable to other types of devices with different safety and efficacy profile. Also, the average age for a stroke onset in Spain might be higher than our

assumption for all patients (68 years), which could potentially lead to an overestimation of health outcomes. However, age was included in the DSA, varied to an upper limit of 81 years, and this did not lead to dramatic changes in the results as the NMB remained positive in all scenarios. Third, patients were assumed to remain in a given mRS score until they experienced a recurrent stroke or death. Other factors that may have an effect on mRS scores, such as comorbidities, were not included. However, this aspect could affect both patient cohorts equally considering there are no differences in the baseline characteristics, nonetheless further studies on mRS decline in the long term are encouraged. Acute and long-term costs were obtained from the original cost-effectiveness model and the same limitations for costs would apply. Finally, resource consumption was based on a panel of experts' consensus and clinical practice and subject to heterogeneity between centres. However, these assumptions were tested in the DSA and PSA and did not alter the overall results.

CONCLUSION

Achieving FPE after MT can lead to important health care cost-saving and better functional clinical outcomes per patient compared to not achieving FPE. Costs saving to the Spanish NHS ranged from -€16,583 to -€44,289 depending on the patient cohort and long-term costs. Increasing FPE rates will lead to greater cost savings to the health care system.

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Figure Legends

Figure 1. mRS outcomes at 90 days Base case and Alternative Scenario.

Acronyms: FPE (First Pass Effect); mRS (modified Rankin Score);

Figure 2. Tornado diagram of deterministic sensitivity analysis

Acronyms: FPE (First Pass Effect); mRS (modified Rankin Score); RR (Relative Risk)

Figure 3. Probabilistic sensitivity analysis

Acronyms: QALYs (Quality-Adjusted Life Years).

1

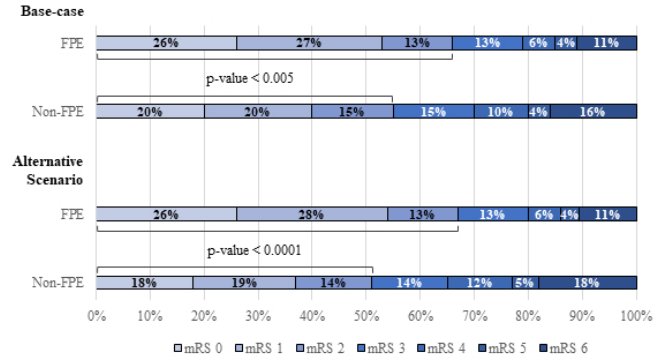

Figure 1 - mRS outcomes at 90 days Base case and Alternative Scenario. Acronyms: FPE (First Pass Effect); mRS (modified Rankin Score).

190x275mm (96 x 96 DPI)

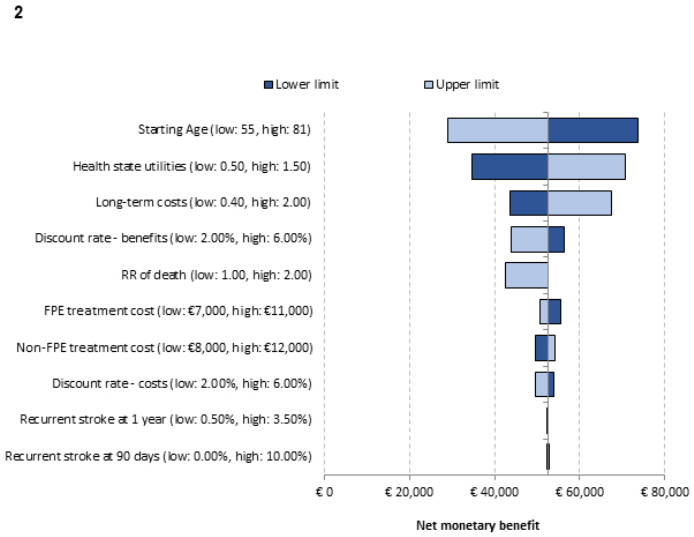

Figure 2 - Tornado diagram of deterministic sensitivity analysis. Acronyms: FPE (First Pass Effect); mRS (modified Rankin Score); RR (Relative Risk)

190x275mm (96 x 96 DPI)

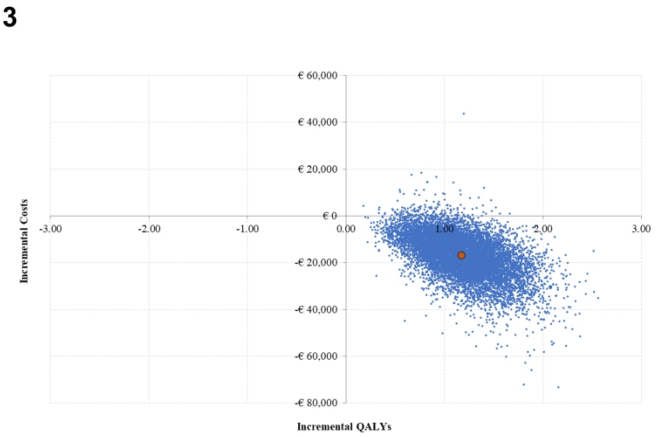

Figure 3 - Probabilistic sensitivity analysis. Acronyms: QALYs (Quality-Adjusted Life Years).

190x275mm (600 x 600 DPI)

Table A1. Relative risk of death by mRS [1]

mRS score	RR
mRS 0	1.00
mRS 1	1.00
mRS 2	1.12
mRS 3	1.66
mRS 4	1.92
mRS 5	2.57

Table A2. Lifetable Spain by age and gender [2]

Other-cause mortality		
Age	**Male**	**Female**
0	0.276%	0.245%
1	0.023%	0.018%
2	0.013%	0.008%
3	0.012%	0.009%
4	0.014%	0.007%
5	0.010%	0.009%
6	0.007%	0.006%
7	0.007%	0.005%
8	0.009%	0.007%
9	0.007%	0.004%
10	0.007%	0.006%
11	0.008%	0.007%
12	0.007%	0.007%
13	0.010%	0.005%
14	0.008%	0.013%
15	0.013%	0.011%
16	0.021%	0.011%
17	0.016%	0.015%
18	0.030%	0.014%
19	0.026%	0.010%
20	0.029%	0.014%
21	0.034%	0.015%
22	0.030%	0.014%
23	0.037%	0.014%
24	0.039%	0.019%
25	0.032%	0.019%
26	0.048%	0.015%

27	0.036%	0.014%
28	0.049%	0.018%
29	0.055%	0.018%
30	0.046%	0.028%
31	0.054%	0.022%
32	0.048%	0.022%
33	0.052%	0.025%
34	0.062%	0.031%
35	0.062%	0.034%
36	0.066%	0.033%
37	0.065%	0.036%
38	0.071%	0.042%
39	0.082%	0.044%
40	0.091%	0.052%
41	0.098%	0.059%
42	0.107%	0.059%
43	0.123%	0.073%
44	0.120%	0.069%
45	0.143%	0.087%
46	0.169%	0.095%
47	0.191%	0.112%
48	0.228%	0.110%
49	0.244%	0.143%
50	0.289%	0.149%
51	0.325%	0.162%
52	0.349%	0.173%
53	0.388%	0.211%
54	0.473%	0.220%
55	0.517%	0.233%
56	0.557%	0.259%
57	0.601%	0.286%
58	0.675%	0.312%
59	0.720%	0.339%
60	0.803%	0.364%
61	0.895%	0.384%
62	0.977%	0.420%
63	1.055%	0.451%
64	1.116%	0.496%
65	1.219%	0.504%
66	1.318%	0.574%
67	1.436%	0.616%
68	1.514%	0.620%

69	1.700%	0.720%
70	1.911%	0.787%
71	1.990%	0.849%
72	2.215%	0.937%
73	2.370%	1.051%
74	2.627%	1.233%
75	2.872%	1.403%
76	3.074%	1.570%
77	3.492%	1.763%
78	4.139%	2.142%
79	4.500%	2.474%
80	5.153%	2.928%
81	5.708%	3.368%
82	6.436%	3.838%
83	7.209%	4.440%
84	8.410%	5.257%
85	9.184%	6.197%
86	10.539%	7.184%
87	11.846%	8.422%
88	13.304%	9.728%
89	15.057%	11.340%
90	16.914%	13.272%
91	19.683%	14.947%
92	20.636%	16.507%
93	23.300%	18.967%
94	25.526%	21.541%
95	27.536%	23.666%
96	29.487%	26.675%
97	31.265%	28.241%
98	32.711%	29.794%
99	26.429%	30.496%
100	48.238%	46.382%

Table A3. Recurrent Stroke Rates [3]

Year	Recurrent Stroke Rate
Year 1	4.91%
Year 2 onwards	2.01%

Table A4. Health States Utilities [4]

mRS	Utility
mRS 0	0.936
mRS 1	0.817
mRS 2	0.681
mRS 3	0.558
mRS 4	0.265
mRS 5	-0.054
mRS 6	0

Table A5. Unit costs, consumption and total management costs for each group of patients [5] [6]

AIS diagnosis + IV-tPA (tPA 30% of patients)			
Item	**Unit cost (€)**	**Units**	**Total cost (€)**
Neurologist	36.19	1.0	36.19
Neuroradiologist	36.19	0.5	18.09
Resident Doctor	12.56	1.0	12.56
Nurse 1	22.01	0.5	11.01
Nurse 2	22.01	0.5	11.01
Technician	17.54	0.5	8.77
Cranial CT scan	84.83	1.0	84.83
Blood test	46.10	1.0	46.10
Electrocardiogram	40.26	1.0	40.26
Chest Radiograph	26.58	0.5	13.29
Computerized tomography angiography	279.25	1.0	279.25
Perfusion computerized tomography	252.17	0.5	126.08
Nursing Assistant 1	13.07	0.5	4.71
Orderly	13.07	0.5	6.53
Alteplase (0,9 mg/kg; average patient weight 75 kg), (30% of the patients)	9.85	67.5	199.67
MRI (0.5% of the patients)	204.48	0.05	3.07
Costs group "FIRST PASS"			
Stent retriever	3.388	1.0	3.388
Intracranial catheter	2.178	1.0	2.178
Ballon guide catheter/ Long Sheath	786.5	1.0	786,5
Guide/Microguide (0.35/0.12/0.14)	484	1.0	484
Microcatheter	605	1.0	605
Introducer	15.73	1.0	15.73
Procedure pack + gloves	32.05	1.0	32.05
Vascular closure device	187.67	1.0	187.67
Diagnosis catheter + contrast	50.05	1.0	50.05

PTA balloon catheter	250.23	0.3	75.07
Carotid stent	1,376.25	0.15	206.44
Anesthetist	36.19	3.0	108.56
Neurologist	36.19	0.2	7.24
Neuroradiologist	36.19	3.0	108.56
Orderly	13.07	0.5	6.53
Nurse	22.01	6.0	132.07
Cranial computerized tomography scan	84.83	1.0	84.83
Costs group "Non-FIRST PASS"			
Stent retriever	3,388	1.20	4,065.60
Intracranial catheter	2,178	1.20	2,613.60
Balloon guide catheter/ Long Sheath	786.5	1.00	786.50
Guide/Microguide (0.35/0.12/0.14)	484	1.20	580.80
Microcatheter	605	1.10	665.50
Introducer	15.73	1.00	15.73
Procedure pack + gloves	32.05	1.00	32.05
Vascular closure device	187.67	1.00	187.67
Diagnosis catheter + contrast	50.05	1.00	48,40
PTA balloon catheter	250.23	0.30	75.07
Carotid stent	1,376.25	0.15	206.44
Anesthetist	36.19	4.00	144.75
Neurologist	36.19	0.20	7.24
Neuroradiologist	36.19	4.00	144.75
Orderly	13.07	0.5	6.53
Nurse	22.01	8.00	176.09
Cranial computerized tomography scan	84.83	1.00	84.83

Table A6 – Subject Demographics and Baseline Characteristics (Base-case Population) [7]

Characteristic	FPE (N=304)	Non FPE (N=350)	P value (FPE vs. non FPE)
Age (years)	69.9±14.93(304) 72.0(61-80)	66.7±14.70(350) 68.0(58-79)	0.7771
Sex (Male)	162/304(53.3%)	189/350(54.0%)	0.8558
Pre-stroke mRS			0.0152
0	220/304(72.4%)	280/350(80.0%)	
1	72/304(23.7%)	63/350(18.0%)	
2*	12/304(3.9%)	7/350(2.0%)	
Initial Qualifying NIHSS Score (Baseline NIHSS)	17.0±5.41(304) 17.0(13-21)	17.3±5.54(350) 18.0(12-21)	0.6769
Total ASPECTS Score	8.3±1.53(266) 9.0(8-9)	8.1±1.59(303) 8.0(8-9)	0.4737
IV tPA administered	181/304(59.5%)	237/350(67.7%)	0.0299
IA-tPA used	29/303(9.6%)	63/348(18.1%)	0.0018
General Anesthesia Used (Site-Reported)	78/303(25.7%)	109/348(31.3%)	0.1166
Stroke onset to puncture (min)	226.6±99.90(301) 215.0(150-295)	217.4±99.33(349) 194.0(143-278)	0.9172

Summary statistics: Mean±SD(n), Median (IQR) for continuous and n/N (%) for categorical variables.

*Patients with Pre-mRS of 2 are enrolled under Rev B protocol.

Each P-value was based on T test (2-sided) for the mean difference and Z test (2-sided) for the proportion difference between FPE and non FPE;mRS scores between FPE and Non-FPE are compared using using Mantel-Haenszel Chi-square test.

Table A7 – Subject Demographics and Baseline Characteristics (Alternative scenario Population) [7]

Characteristic	FPE (N=317)	Non FPE (N=431)	P value (FPE vs. non FPE)
Age (years)	69.7±14.85(317) 72.0(61-80)	67.1±14.61(431) 68.0(58-79)	0.7459
Sex (Male)	170/317(53.6%)	225/431(52.2%)	0.6999
Pre-stroke mRS			0.0380
0	230/317(72.6%)	340/431(78.9%)	
1	75/317(23.7%)	81/431(18.8%)	
2*	12/317(3.8%)	10/431(2.3%)	
Initial Qualifying NIHSS Score (Baseline NIHSS)	17.1±5.41(317) 17.0(13-21)	17.3±5.54(431) 18.0(12-21)	0.6550
Total ASPECTS Score	8.3±1.51(275) 9.0(8-9)	8.1±1.65(378) 8.0(7-9)	0.1184
IV tPA administered	193/317(60.9%)	285/431(66.1%)	0.1402
IA-tPA used	31/316(9.8%)	79/428(18.5%)	0.0010
General Anesthesia Used (Site-Reported)	80/316(25.3%)	138/428(32.2%)	0.0402
Stroke onset to puncture (min)	227.2±100.86(314) 213.5(150-295)	222.9±101.11(428) 199.5(146-290)	0.9660

Summary statistics: Mean±SD(n), Median (IQR) for continuous and n/N (%) for categorical variables.

*Patients with Pre-mRS of 2 are enrolled under Rev B protocol.

Each P-value was based on T test (2-sided) for the mean difference and Z test (2-sided) for the proportion difference between FPE and non FPE;mRS scores between FPE and Non-FPE are compared using using Mantel-Haenszel Chi-square test.

Table A8 – Medical and Neurological History (Base-case Population) [7]

	FPE (N=304)	Non FPE (N=350)	P value (FPE vs. non FPE)
Atrial flutter/Atrial fibrillation	128/304(42.1%)	120/350(34.3%)	0.0398
Systemic Hypertension	217/304(71.4%)	262/350(74.9%)	0.3166
Diabetes mellitus	91/304(29.9%)	93/350(26.6%)	0.3401
Myocardial disease/Coronary artery disease	95/304(31.3%)	85/350(24.3%)	0.0467
Hyperlipidemia	129/304(42.4%)	155/350(44.3%)	0.6337
Peripheral artery disease	13/304(4.3%)	13/350(3.7%)	0.7137
Carotid artery disease	33/304(10.9%)	17/350(4.9%)	0.0040
Current or former tobacco use	137/304(45.1%)	162/350(46.3%)	0.7548
Neurological history			
Previous ischemic stroke	43/304(14.1%)	34/350(9.7%)	0.0795
Previous hemorrhagic stroke	3/304(1.0%)	3/350(0.9%)	0.8622
Previous TIA	20/304(6.6%)	17/350(4.9%)	0.3418
Brain aneurysm	3/304(1.0%)	1/350(0.3%)	0.2514

Summary Statistics for categorical: n/N (%)

Each P-value was based on Z test (2-sided) for the proportion difference between FPE and non-FPE

Table A9 – Medical and Neurological History (Alternative scenario Population) [7]

	FPE (N=317)	Non FPE (N=431)	P value (FPE vs. non FPE)
Atrial flutter/Atrial fibrillation	134/317(42.3%)	152/431(35.3%)	0.0514
Systemic Hypertension	223/317(70.3%)	327/431(75.9%)	0.0907
Diabetes mellitus	91/317(28.7%)	111/431(25.8%)	0.3688
Myocardial disease/Coronary artery disease	96/317(30.3%)	112/431(26.0%)	0.1948
Hyperlipidemia	132/317(41.6%)	192/431(44.5%)	0.4278
Peripheral artery disease	13/317(4.1%)	16/431(3.7%)	0.7856
Carotid artery disease	35/317(11.0%)	27/431(6.3%)	0.0192
Current or former tobacco use	143/317(45.1%)	202/431(46.9%)	0.6338
Neurological history			
Previous ischemic stroke	46/317(14.5%)	43/431(10.0%)	0.0584
Previous hemorrhagic stroke	3/317(0.9%)	4/431(0.9%)	0.9795
Previous TIA	20/317(6.3%)	22/431(5.1%)	0.4794
Brain aneurysm	4/317(1.3%)	3/431(0.7%)	0.4271

Summary Statistics for categorical: n/N (%)

Each P-value was based on Z test (2-sided) for the proportion difference between FPE and non-FPE

Table A10. Adverse events Base-Case and alternative scenario

Patient group **Base case**	**symptomatic intracranial hemorrhage***	**malignant cerebral edema**
FPE	0.7%	1%
Non-FPE	2.3%	1.4%
P-values are obtained from Fisher's exact test	0.1154	0.7303
Patient group **Alternative Scenario**	**symptomatic intracranial hemorrhage**	**malignant cerebral edema**
FPE	0.6%	0.9%
Non-FPE	2.1%	1.4%
P-values are obtained from Fisher's exact test.	0.1297	0.7403
*sICH is defined as any PH1, PH2, RIH, IVH or SAH per imaging core lab and associated with ≥ 4 points worsening on the NIHSS scale within 24 hours.		

References:

1. Slot KB, Berge E, Sandercock P, et al. Causes of death by level of dependency at 6 months after ischaemic stroke in 3 large cohorts. Stroke 2009; 40: 1585–1589.
2. Instituto Nacional de Estadıstica. 2018 Mortality tables of Spanish population. National results. In: INEbase. [Internet]. 2018 [cited 2020 Oct 10]. Available from: www.ine.es
3. Mohan KM, Wolfe CDA, Rudd AG, Heuschmann PU, Kolominsky-Rabas PL, Grieve AP. Risk and cumulative risk of stroke recurrence: A systematic review and meta-analysis. Stroke. 2011;42(5):1489–94. E
4. Rivero-Arias O, Ouellet M, Gray A, Wolstenholme J, Rothwell PM, Luengo-Fernandez R. Mapping the modified rankin scale (mRS) measurement into the generic EuroQol (EQ-5D) health outcome. Med Decis Mak. 2010;30(3):341–54.
5. de Andrés-Nogales F, Álvarez M, de Miquel MÁ, Segura T, Gil A, Cardona P, et al. Cost-effectiveness of mechanical thrombectomy using stent retriever after intravenous tissue plasminogen activator compared with intravenous tissue plasminogen activator alone in the treatment of acute ischaemic stroke due to large vessel occlusion in Spa. Eur Stroke J. 2017;2(3):272–84.
6. Expert opinion
7. Mueller-Kronast NH, Zaidat OO, Froehler MT, Jahan R, et al. Systematic Evaluation of Patients Treated With Neurothrombectomy Devices for Acute Ischemic Stroke: Primary Results of the STRATIS Registry. Stroke. 2017;48(10):2760–8.

CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force*, provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Lines 1-2
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Lines 44-71
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	Lines 95-115 Lines 117-119
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Lines 147-153
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Line 128
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Line 128 Lines 180-182
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Lines 126-130
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Line 130
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Lines 191-193
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Lines 199-202
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	NA

	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	NA
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	NA
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	NA
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Lines 182-193
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Lines 191-192
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Lines 134-144
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Lines 134-144
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Lines 144-145 Lines 161-164 Lines 204-211
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Table 1 Tables A1 - A9
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Table 2
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	NA

		of methodological assumptions (such as discount rate, study perspective).	NA
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Lines 263-270
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Table 2
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Lines 282-316 Lines 343-361
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Lines 375-376
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Lines 378-383

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

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