

# BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email [info.bmjopen@bmj.com](mailto:info.bmjopen@bmj.com)

# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-054816
Article Type:	Original research
Date Submitted by the Author:	23-Jun-2021
Complete List of Authors:	González Diaz, Eva; Cruces University Hospital, Neurointerventional radiology, Radiology department Rodríguez-Paz, Carlos; Hospital Álvaro Cunqueiro, Neuroradiology Unit, Department of Radiology Fernandez-Prieto, Andres; Hospital Universitario La Paz, Neurointerventional radiology, Radiology department Martínez-Galdámez, Mario; University Clinical Hospital of Valladolid, Neuroradiology Unit Martínez-Moreno, Rosa; Hospital Universitario Virgen de las Nieves Ortega Quintanilla, Joaquín; Hospital Universitario Virgen del Rocío Tomasello, Alejandro; Vall d'Hebron University Hospital, Interventional Neuroradiology Section, Department of Radiology; Vall d'Hebron University Hospital, Vall d'Hebron Research Institute (VHIR) Zamarro, Joaquín; Hospital Clínico Universitario Virgen de la Arrixaca, Interventional Neuroradiology Liebeskind, David; University of California Los Angeles, Neurovascular Imaging Core and UCLA Stroke Center, Department of Neurology Zaidat, Osama; St Vincent Mercy Hospital Mueller-Kronast, nils; Advanced Neuroscience Network/Tenet South Florida
Keywords:	HEALTH ECONOMICS, Stroke < NEUROLOGY, Interventional radiology < RADIOLOGY & IMAGING, Neuroradiology < NEUROLOGY

SCHOLARONE™  
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1  
2  
3 **1 Economic analysis of the first pass effect in mechanical thrombectomy for acute ischemic**  
4 **stroke treatment in Spain.**  
5  
6  
7  
8  
9

10 4 Eva González-Díaz<sup>1</sup>, MD; Carlos Rodríguez-Paz<sup>2</sup>, MD; Andres Fernandez-Prieto<sup>3</sup>, MD; Mario  
11  
12 5 Martínez-Galdámez<sup>4</sup>, MD; Rosa Martínez-Moreno<sup>5</sup>, MD; Joaquín Ortega Quintanilla<sup>6</sup>, MD;  
13  
14 6 Alejandro Tomasello<sup>7,8</sup>, MD; Joaquín Zamarró<sup>9</sup>, MD; David S. Liebeskind, MD<sup>10</sup>; Osama O.  
15  
16 7 Zaidat<sup>11</sup>, MD, MS; Nils H. Mueller-Kronast, MD<sup>12</sup>.  
17  
18  
19  
20  
21  
22  
23  
24  
25

26 11 <sup>1</sup>Neurointerventional radiology, Radiology department, Cruces University Hospital, Barakaldo,  
27  
28 12 Basque Country, Spain.  
29

30 13 <sup>2</sup>Neuroradiology Unit, Department of Radiology, Hospital Álvaro Cunqueiro, Vigo, Spain  
31

32 14 <sup>3</sup>Neurointerventional radiology, Radiology department, Hospital Universitario La Paz, Madrid,  
33  
34 15 Spain.  
35  
36

37 16 <sup>4</sup>Neuroradiology Unit, University Clinical Hospital of Valladolid, Valladolid, Spain  
38

39 17 <sup>5</sup>Hospital Universitario Virgen de las Nieves, Granada, Spain.  
40

41 18 <sup>6</sup>Interventional Neuroradiology, Hospital Universitario Virgen del Rocío, Sevilla, Andalucía,  
42  
43 19 Spain  
44

45 20 <sup>7</sup>Interventional Neuroradiology Section, Department of Radiology, Vall d'Hebron University  
46  
47 21 Hospital, Barcelona, Spain.  
48

49 22 <sup>8</sup>Vall d'Hebron Research Institute (VHIR), Vall d'Hebron University Hospital, Barcelona,  
50  
51 23 Spain  
52

53 24 <sup>9</sup>Interventional Neuroradiology, Hospital Clinico Universitario Virgen de la Arrixaca, Murcia,  
54  
55 25 Spain  
56  
57  
58  
59  
60

1  
2  
3 26 <sup>10</sup> Neurovascular Imaging Core and UCLA Stroke Center, Department of Neurology,  
4  
5 27 University of California Los Angeles, Los Angeles, California, USA  
6  
7

8 28 <sup>11</sup> St Vincent Mercy Hospital, Toledo, Ohio, USA  
9

10 29 <sup>12</sup> Advanced Neuroscience Network/Tenet South Florida, Delray Beach, Florida, USA  
11  
12  
13  
14  
15  
16  
17  
18

19 33 **Corresponding author:** Eva González-Díaz, [evagonzalezdiaz@yahoo.com](mailto:evagonzalezdiaz@yahoo.com),  
20  
21 34 Neurointerventional Radiology, Radiology department, Cruces University Hospital, Plaza  
22  
23 35 Cruces S/N 48903, Barakaldo, Basque Country, Spain, +34669309168  
24  
25  
26  
27  
28  
29  
30  
31  
32

33 39 **Keywords:** First-pass effect, health economics, ischaemic stroke, mechanical thrombectomy,  
34  
35 40 net monetary benefit, reperfusion, Spain  
36  
37

38 41 **Word count:** 2,498  
39

40 42 **Total number of tables and figures:** 2 Tables, 3 Figures  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## 44 **Abstract**

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

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

59 **Setting:** Spanish healthcare perspective.

60 **Participants:** AIS patients in Spain.

61 **Interventions:** FPE following MT.

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

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

1  
2  
3 68 group. Cost-savings and QALY gains were greater in the alternative scenario (-€44,289; 1.75).

4  
5 69 In all scenarios, cost-savings were driven by the long-term cost reduction.

6  
7  
8 70 **Conclusion:** Achieving FPE after MT can lead to better health outcomes per AIS patient. and

9  
10 71 important cost-savings for the Spanish NHS.

11  
12 72

13  
14 73

## 15 74 **Article Summary**

16  
17 75 Strengths and limitations of this study

18  
19 76 • A Markov model estimated the lifetime health and cost implications of achieving FPE  
20  
21  
22  
23 77 in AIS patients treated with Mechanical Thrombectomy in Spain from the NHS  
24  
25  
26 78 perspective.

27  
28 79 • The model allows to quantify the benefits of aiming mechanical thrombectomy  
29  
30  
31 80 techniques that may increase the first pass effect success rates.

32  
33 81 • A limitation of this study is that clinical efficacy and patient characteristics were based  
34  
35  
36 82 on the STRATIS registry, which included centers outside Spain.

37  
38 83 • Another limitation is that some model parameters, such as acute and long-term costs  
39  
40  
41 84 have been derived from literature, which have been validated by clinical experts.

42  
43 85

44  
45 86

46  
47 87

48  
49 88

50  
51 89

52  
53 90

54  
55 91

56  
57 92

58  
59  
60

## 93 INTRODUCTION

94

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

101

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

108

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

116



1  
2  
3 117 The objective of this study is to assess the health outcome benefits and economic impact of  
4  
5 118 achieving FPE for the AIS patients from the National Health System (NHS) perspective in  
6  
7  
8 119 Spain.  
9

10 120

11  
12 121

13  
14  
15 122

## 16 17 123 **METHODS**

18  
19 124

### 20 21 125 **Model structure**

22  
23  
24 126 A previously published cost-effectiveness model comparing MT + IV-tPA with IV-tPA alone  
25  
26 127 in a Spanish NHS setting was modified to reflect only patients that received MT treatment  
27  
28 128 which afterwards were stratified to reflect those who achieved FPE and those who didn't (Non-  
29  
30 129 FPE) (5), and allowed to estimate lifetime health and costs outcomes of the two patient groups.  
31  
32  
33 130 As in the previous modelling, this analysis is also over the patient's lifetime and from the  
34  
35 131 Spanish NHS perspective. The model was developed using Microsoft Excel (Microsoft  
36  
37 132 Corporation, Redmond, WA, USA).  
38  
39

40 133

41  
42 134 The model had a two-phase structure, consisting of an acute-subacute phase from stroke onset  
43  
44 135 to 90 days, and a rest-of-life phase 91 days after stroke to the end of patient's life. In the acute-  
45  
46 136 subacute phase, patients enter the model once reperfusion status (FPE vs Non-FPE) has been  
47  
48  
49 137 determined, and then are assigned to one of the seven mutually exclusive health states based  
50  
51 138 on Modified Ranking Scale (mRS; 0-no symptoms, 6-death) to reflect several degrees of  
52  
53 139 disability at 90 days. Afterwards, patients enter a Markov structure, from 91 days after the  
54  
55  
56 140 stroke to the end of the patients' life. In this phase, patients could remain in the same health  
57  
58 141 state or transition to different states during each annual cycle until the end of life, depending  
59  
60

1  
2  
3 142 on the occurrence of a recurrent stroke or death from other causes (age-gender specific  
4  
5 143 mortality). A half-cycle correction was used to account for transitions occurring in the middle  
6  
7  
8 144 of a cycle.  
9

10 145

### 11 12 146 **Patient population**

13  
14 147 The model simulates a hypothetical cohort of 1,000 patients with clinic-demographic  
15  
16 148 characteristics based on the STRATIS registry (Systematic Evaluation of Patients Treated With  
17  
18 149 Neurothrombectomy Devices for Acute Ischemic Stroke) (12). The base-case analysis  
19  
20 150 stratified patients into FPE and Non-FPE groups considering STRATIS registry patients that  
21  
22 151 achieved a final mTICI $\geq$ 2b. The alternative scenario included all STRATIS registry patients  
23  
24 152 regardless of their final mTICI (0-3).  
25  
26  
27

28 153

### 29 30 154 **Clinical data**

31  
32 155 Clinical data was obtained from a sub-analysis of the STRATIS registry (12) in which FPE and  
33  
34 156 Non-FPE groups were compared. Moreover, it was considered that patients were at risk of  
35  
36 157 experiencing adverse events (symptomatic intracranial hemorrhage and malignant cerebral  
37  
38 158 edema) during the acute-subacute phase, therefore adverse events data was also obtained from  
39  
40 159 STRATIS registry sub-analysis.  
41  
42  
43

44 160

45  
46 161 Categorical variables were compared using  $\chi^2$  (Chi-square) test and Mantel-Haenszel Chi-  
47  
48 162 square test when appropriate. Proportion differences were compared by z-test both one-sided  
49  
50 163 and two-sided tests are performed (considering 5% and 2.5% significance level respectively).  
51  
52

53 164 All statistical analyses were performed using SAS version 9.4.  
54  
55

56 165  
57  
58  
59  
60

1  
2  
3 166 Background age-gender related mortality was obtained from the latest available Life Table in  
4  
5 167 Spain (data from 2018) (13) and relative risks of death by mRS score were used to adjust age-  
6  
7  
8 168 gender-related mortality (14) to account for the increased risks observed among stroke  
9  
10 169 survivors (Supplementary Material Table A1 & A2). Recurrence stroke rates were obtained  
11  
12 170 from Mohan et al. (15) (Supplementary Material (Table A3)).  
13  
14

15 171

### 17 172 **Quality of life**

18  
19 173 Health outcomes were measured using quality-adjusted life years (QALY), a measure that  
20  
21 174 weights life-years gained with an intervention by its utility value. Utilities assigned to health  
22  
23 175 states can take values from 0 (death) to 1 (optimal health) and negative values (state worse than  
24  
25 176 death). Utilities by mRS score were obtained from Rivero-Arias et al. 2010 (16), with values  
26  
27 177 ranging from 0.93 (mRS 0) to -0.54 (mRS 5) (Supplementary Material (Table A4)).  
28  
29  
30

31 178

### 33 179 **Costs**

34  
35 180 The study considered the Spanish NHS perspective, consequently, only direct medical costs  
36  
37 181 were considered, including treatment and adverse events management costs, acute and long-  
38  
39 182 term care costs. Treatment costs were updated to reflect the costs for each patient group (FPE  
40  
41 183 vs Non-FPE) and were kept in line with the new treatment approaches according to local  
42  
43 184 practice based on a panel of experts' consensus. Treatment costs in both groups FPE and Non-  
44  
45 185 FPE included the costs of AIS diagnosis, and adjunctive IV-tPA in 30% of the cases according  
46  
47 186 to local practice (Table A5, Supplementary Material).  
48  
49  
50

51 187

52  
53 188 Adverse events, acute and long-term costs by mRS score were kept consistent with the previous  
54  
55 189 model (5). For each scenario, a second analysis was performed to include formal care costs  
56  
57 190 such as nursing/residential costs. All costs are presented in Euros and were inflated to reflect  
58  
59  
60

1  
2  
3 191 Euros in 2020 (Table 1). Costs and health outcomes were discounted at an annual discount rate  
4  
5 192 of 3% consistent with the relevant health technology assessment guidelines for Spain (17).  
6  
7  
8 193

9  
10 194 **Table 1. Adjusted Acute and long-term costs (Euros 2020)**  
11

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		

195  
196 *Note: Table adapted from De Andrés-Nogales et al., 2017 (6)*  
197

### 198 **Economic model outcomes and sensitivity analysis**

199 The model estimates the lifetime total costs and QALYs for each patient group. To quantify  
200 the net economic value of FPE, the net monetary benefit (NMB) was calculated, considering a  
201 willingness-to-pay (WTP) threshold of €30,000/QALY, (NMB=(Incremental QALYs×WTP)-  
202 Incremental Costs) (18,19).  
203

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

1  
2  
3 209 parameters simultaneously (mRS scores at 90 days (Dirichlet), mortality relative risks  
4  
5 210 (Lognormal), starting age (Normal), utilities (Beta) and costs (Gamma)), to account for the  
6  
7  
8 211 general uncertainty around model inputs (5).  
9

10 212

### 12 213 **Patient and public involvement**

14 214 This study was conducted without patient and public involvement. Therefore, patients were not  
15  
16  
17 215 involved in the study design, reporting or interpretation of the findings. This study included a  
18  
19 216 post-hoc analysis of an existing study, therefore institutional review board approval was not  
20  
21 217 obtained for this analysis. Moreover, no research approval was required for model input  
22  
23  
24 218 parameters that were obtained from literature or based on panel of experts consensus.  
25

26 219

28 220

30 221

## 32 222 **RESULTS**

34 223

36 224 Based on STRATIS sub-analysis, the mean age of stroke considered in the model was 68 years.

38 225 Both groups have similar characteristics at baseline. Descriptive statistics on the FPE and Non-

40 226 FPE groups are reported in Supplementary Material, Tables A6-A7-A8-A9.

42 227 Our results suggest that the FPE group had significantly better clinical outcomes at 90 days

44 228 after stroke compared to the Non-FPE group in the base-case scenario (mRS 0-2: 66.2% vs

46 229 54.6%,  $p$ -value<0.005). Similar results in the alternative scenario were observed (mRS 0-2:

48 230 66.9% vs 50.6%,  $p$ -value<0.0001) (Figure 1). Adverse events results across scenario

50 231 populations are presented in the Supplementary Material (Table A10).  
51  
52  
53

54 232

**[Insert Figure 1]**

233 In the base-case scenario, the model estimates an average lifetime cost per patient equal to  
 234 €97,206 for the FPE group and €113,790 for the Non-FPE group. Of these, 83% were  
 235 associated with long-term costs. Overall, the FPE group generated a cost reduction of €16,583  
 236 per patient in a lifetime horizon. Cost reductions are predicted to be greater when  
 237 nursing/residential care cost are included, leading to a savings of €30,072 per patient.

238

239 In terms of health outcomes, the model estimates that achieving FPE lead to a QALY gain of  
 240 1.2 years (7.89 vs 6.69), while the number of independent people at 90 days is also projected  
 241 to increase by 116 (662 vs 546) in this hypothetical cohort. However, there is an estimated  
 242 increase in the total number of recurrent strokes in the FPE group due to patients living longer  
 243 (283 vs 257).

244

245 The model suggests that achieving FPE lead to a NMB of €52,634 considering a WTP of  
 246 €30,000/QALY gained. The NMB was expected to increase to €66,122 when  
 247 nursing/residential care cost are considered. FPE provides greater net economic value  
 248 demonstrating higher efficacy with lower costs from the payer perspective in a lifetime time  
 249 horizon (Table 2). In the alternative scenario, similar results were observed, which may confirm  
 250 the greater benefits that achieving FPE (between 32%-47% higher) may provide when all  
 251 patients regardless their final mTICI are considered (QALY gain of 1.75 years and €21,910  
 252 cost reduction; when considering nursing/residential costs, a cost reduction of €44,289 and a  
 253 NMB of €96,684) (Table 2).

254

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

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

11

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
<b>Total costs (€)</b>	<b>97,206</b>	<b>113,790</b>	<b>-16,583</b>	<b>95,925</b>	<b>117,836</b>	<b>-21,910</b>
NMB (€)			52,634			74,306
<b>Total costs (With nursing/residential care cost) (€)</b>	<b>161,982</b>	<b>192,054</b>	<b>-30,072</b>	<b>159,565</b>	<b>203,854</b>	<b>-44,289</b>
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

256

257

### 258 Sensitivity analysis

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

266

**[Insert Figure 2]**

267

**[Insert Figure 3]**

268

269

## 270 DISCUSSION

271

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

276

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

285

286 The base-case results suggest that achieving FPE yields better health outcomes than Non-FPE  
287 group, providing an incremental QALY gain of 1.2 (in alternative scenario, QALY gain of  
288 1.75), equivalent to 438 days in perfect health (657 days for alternative scenario). From the  
289 cost perspective, both scenarios suggest that the FPE group is associated with lower health care  
290 costs, leading to a cost-saving of €16,583 in the base-case scenario, €30,072 when considering  
291 nursing/residential healthcare costs, and -€21,910 to €44,289 in the alternative scenario) (Table  
292 2). Cost savings in both scenarios were mainly driven by reductions in long-term costs  
293 associated with the management of functionally dependent patients. Furthermore, all results  
294 were tested by performing DSA and PSA which demonstrated that our results are robust. In



1  
2  
3 295 both scenarios and sub-scenarios, the Non-FPE group was associated with lower health benefits  
4  
5 296 and higher health care costs.  
6  
7  
8 297

9  
10 298 A recently published study (21) estimated the short-term cost implications of FPE in several  
11  
12 299 countries, including Spain. The authors estimated the procedural/hospitalization and annual  
13  
14 300 care costs differences considering a 1-year time horizon. Similar to our work, the study showed  
15  
16 301 lower procedural/hospitalization and annual care costs for patients that achieved FPE vs. Non-  
17  
18 302 FPE across countries considered. Furthermore, our findings are compatible with other studies  
19  
20 303 undertaken in the United States that have demonstrated that achieving TICI 3 lead to healthcare  
21  
22 304 and societal cost savings relative to achieving TICI 2b for LVO (22,23).  
23  
24  
25  
26 305

27  
28 306 Overall, the results of this study showed that raising the FPE rate will not only increase the  
29  
30 307 quality of life for patients, but also decrease the overall health care costs. Achieving FPE can  
31  
32 308 potentially be one of the primary goals in the treatment of patients with ischemic stroke due to  
33  
34 309 LVO from both a clinical and economic perspective. Because this analysis was performed from  
35  
36 310 the Spanish NHS perspective, only the direct costs are considered. There could be larger  
37  
38 311 savings associated with achieving FPE if indirect costs, such as informal care and productivity  
39  
40 312 losses, were included.  
41  
42  
43  
44 313

45  
46 314 To our knowledge, this is one of the first studies that aim to evaluate the lifetime health and  
47  
48 315 cost implications of achieving FPE in AIS patients in Spain from the NHS perspective. Among  
49  
50 316 the strengths of this study are the Markov structure (allows to better reflect the patient pathway  
51  
52 317 in terms of lifetime costs and benefits) and the inclusion of comprehensive diagnostics and  
53  
54 318 treatments costs, main adverse events management, and recurrent strokes, to account for all  
55  
56 319 health outcomes and associated costs after a stroke.  
57  
58  
59  
60

1  
2  
3 320  
4

5 321 This study has some limitations. First, clinical efficacy and patient characteristics were based  
6  
7 322 on the STRATIS registry, which included centers outside Spain. Furthermore, the STRATIS  
8  
9 323 registry is based on specific stent retrievers and might not be applicable to other types of  
10  
11 324 devices with different safety and efficacy profile. Also, the average age for a stroke onset in  
12  
13 325 Spain might be higher than our assumption for all patients (68 years), which could potentially  
14  
15 326 lead to an overestimation of health outcomes. However, age was included in the DSA, varied  
16  
17 327 to an upper limit of 75 years, and this did not lead to dramatic changes in the results as the  
18  
19 328 NMB remained positive in all scenarios. Third, patients were assumed to remain in a given  
20  
21 329 mRS score until they experienced a recurrent stroke or death. Other factors that may have an  
22  
23 330 effect on mRS scores, such as comorbidities, were not included. However, this aspect should  
24  
25 331 affect both patient cohorts equally. Acute and long-term costs were obtained from the original  
26  
27 332 cost-effectiveness model and the same limitations for costs would apply. Finally, resource  
28  
29 333 consumption was based on a panel of experts' consensus and clinical practice and subject to  
30  
31 334 heterogeneity between centres. However, these assumptions were tested in the DSA and PSA  
32  
33 335 and did not alter the overall results.  
34  
35  
36  
37  
38  
39

40 336

41 337

42 338

43  
44  
45  
46  
47 339 **CONCLUSION**

48  
49 340 Achieving FPE after MT can lead to important health care cost-saving and better functional  
50  
51 341 clinical outcomes per patient compared to not achieving FPE. Costs saving to the Spanish NHS  
52  
53 342 ranged from -€16,583 to -€44,289 depending on the patient cohort and long-term costs.  
54  
55 343 Increasing FPE rates will lead to greater cost savings to the health care system.  
56  
57  
58

59 344  
60

1  
2  
3 3454  
5 346 **Acknowledgements**6  
7 347 The authors acknowledge Medtronic and Valeska Seguel Ravest for its support and editorial  
8  
9 assistance.  
10 34811  
12 34913  
14 35015  
16 351 **Funding:** This study was sponsored by Medtronic. There is no grant number available for this  
17  
18 study.  
19 35220  
21 35322  
23 35424  
25 355 **Competing interests:** EGD, CRP, AFP, RMM, JOQ, JZ declare no conflicts of interest. MMG  
26  
27 is a proctor and consultant of Medtronic. AT is a consultant, proctor and advisor of Medtronic  
28  
29 (Consultancy Anaconda, Balt, Stryker and Perflow). NHMK is a scientific consultant regarding  
30  
31 trial design and conduct for Medtronic. Ooz is a consultant for Neuravi/Cerenovus, Stryker,  
32  
33 Penumbra, and Medtronic. DSL is an imaging core laboratory consultant for Cerenovus,  
34  
35 Genentech, Medtronic, and Stryker.  
36  
37 36038  
39 36140  
41 36242  
43 363 **Contributors:** EGD, CRP, AFP, RMM, JOQ, JZ, AT and MMG: contributed in the design,  
44  
45 data collection, analysis, interpretation and drafting, reviewing, and revising the manuscript.  
46  
47 NHMK, Ooz and DSL: reviewing and revising the manuscript  
48  
49 36550  
51 36652  
53 36754  
55 368 **Patient consent for publication:** Not required.  
56  
57  
58  
59  
60

1  
2  
3 369 **Data Sharing Statement:** All relevant model inputs used in this study are included in the  
4  
5 370 article and supplement.  
6  
7  
8 371  
9  
10 372

11  
12 373 **References**  
13

- 14 374 1. Stevens, Eleanor; Emmett, Eva; Wang, Yanzhong; McKeivitt, Christopher; Wolfe C.  
15  
16 375 The burden of stroke in Europe report. Stroke Alliance Eur. 2017;131 p.  
17  
18  
19 376 2. Luengo-Fernandez R, Violato M, Candio P, Leal J. Economic burden of stroke across  
20  
21 377 Europe: A population-based cost analysis. Eur Stroke J. 2020;5(1):17–25.  
22  
23  
24 378 3. Turc G, Bhogal P, Fischer U, Khatri P, Lobotesis K, Mazighi M, et al. European  
25  
26 379 Stroke Organisation (ESO) – European Society for Minimally Invasive Neurological  
27  
28 380 Therapy (ESMINT) Guidelines on Mechanical Thrombectomy in Acute Ischaemic  
29  
30 381 Stroke Endorsed by Stroke Alliance for Europe (SAFE). Eur Stroke J. 2019;4(1):6–12.  
31  
32  
33 382 4. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et  
34  
35 383 al. 2018 Guidelines for the Early Management of Patients With Acute Ischemic  
36  
37 384 Stroke: A Guideline for Healthcare Professionals From the American Heart  
38  
39 385 Association/American Stroke Association. Vol. 49, Stroke. 2018. 46–110 p.  
40  
41  
42 386 5. de Andrés-Nogales F, Álvarez M, de Miquel MÁ, Segura T, Gil A, Cardona P, et al.  
43  
44 387 Cost-effectiveness of mechanical thrombectomy using stent retriever after intravenous  
45  
46 388 tissue plasminogen activator compared with intravenous tissue plasminogen activator  
47  
48 389 alone in the treatment of acute ischaemic stroke due to large vessel occlusion in Spa.  
49  
50 390 Eur Stroke J. 2017;2(3):272–84.  
51  
52  
53 391 6. Bai Y, Pu J, Wang H, Yang D, Hao Y, Xu H, et al. Impact of Retriever Passes on  
54  
55 392 Efficacy and Safety Outcomes of Acute Ischemic Stroke Treated with Mechanical  
56  
57  
58  
59  
60

- 1  
2  
3 393 Thrombectomy. *Cardiovasc Intervent Radiol*. 2018;41(12):1909–16.  
4  
5  
6 394 7. Bai X, Zhang X, Yang W, Zhang Y, Wang T, Xu R, et al. Influence of first-pass effect  
7  
8 395 on recanalization outcomes in the era of mechanical thrombectomy: a systemic review  
9  
10 396 and meta-analysis. *Neuroradiology*. 2020;(77).  
11  
12  
13 397 8. Zaidat OO, Castonguay AC, Linfante I, Gupta R, Martin CO, Holloway WE, et al.  
14  
15 398 First pass effect: A new measure for stroke thrombectomy devices. *Stroke*.  
16  
17 399 2018;49(3):660–6.  
18  
19  
20 400 9. Zaidat OO, Haussen DC, Hassan AE, Jadhav AP, Mehta BP, Mokin M, et al. Impact of  
21  
22 401 Stent Retriever Size on Clinical and Angiographic Outcomes in the STRATIS Stroke  
23  
24 402 Thrombectomy Registry. *Stroke*. 2019;50(2):441–7.  
25  
26  
27  
28 403 10. Nguyen TN, Malisch T, Castonguay AC, Gupta R, Sun CHJ, Martin CO, et al. Balloon  
29  
30 404 guide catheter improves revascularization and clinical outcomes with the solitaire  
31  
32 405 device : Analysis of the north american solitaire acute stroke registry. *Stroke*.  
33  
34 406 2014;45(1):141–5.  
35  
36  
37  
38 407 11. Di Maria F, Kyheng M, Consoli A, Desilles JP, Gory B, Richard S, et al. Identifying  
39  
40 408 the predictors of first-pass effect and its influence on clinical outcome in the setting of  
41  
42 409 endovascular thrombectomy for acute ischemic stroke: Results from a multicentric  
43  
44 410 prospective registry. *Int J Stroke*. 2020;16(1):20–8.  
45  
46  
47  
48 411 12. Mueller-Kronast NH, Zaidat OO, Froehler MT, Jahan R, et al. Systematic Evaluation  
49  
50 412 of Patients Treated With Neurothrombectomy Devices for Acute Ischemic Stroke:  
51  
52 413 Primary Results of the STRATIS Registry. *Stroke*. 2017;48(10):2760–8.  
53  
54  
55  
56 414 13. Instituto Nacional de Estadística. 2018 Mortality tables of Spanish population.  
57  
58 415 National results. In: INEbase. [Internet]. 2018 [cited 2020 Oct 10]. Available from:  
59  
60

- 1  
2  
3 416 www.ine.es  
4  
5  
6 417 14. Slot KB, Berge E, Sandercock P, Lewis SC, Dorman P, Dennis M. Causes of death by  
7  
8 418 level of dependency at 6 months after ischemic stroke in 3 large cohorts. *Stroke*.  
9  
10 419 2009;40(5):1585–9.  
11  
12  
13 420 15. Mohan KM, Wolfe CDA, Rudd AG, Heuschmann PU, Kolominsky-Rabas PL, Grieve  
14  
15 421 AP. Risk and cumulative risk of stroke recurrence: A systematic review and meta-  
16  
17 422 analysis. *Stroke*. 2011;42(5):1489–94.  
18  
19  
20  
21 423 16. Rivero-Arias O, Ouellet M, Gray A, Wolstenholme J, Rothwell PM, Luengo-  
22  
23 424 Fernandez R. Mapping the modified rankin scale (mRS) measurement into the generic  
24  
25 425 EuroQol (EQ-5D) health outcome. *Med Decis Mak*. 2010;30(3):341–54.  
26  
27  
28  
29 426 17. López Bastida J, Oliva J, Antoñanzas F, García-Altés A, Gisbert R, Mar J, et al.  
30  
31 427 Propuesta de guía para la evaluación económica aplicada a las tecnologías sanitarias.  
32  
33 428 *Gac Sanit*. 2010;24(2):154–70.  
34  
35  
36 429 18. Sacristán JA, Oliva J, Del Llano J, Prieto L, Pintod JL. Qué es una tecnología  
37  
38 430 sanitaria eficiente en España? *Gac Sanit*. 2002;16(4):334–43.  
39  
40  
41 431 19. De Cock E, Miravittles EM, González-Juanatey JR, Azanza-Perea JR. Valor umbral  
42  
43 432 del coste por año de vida ganado para recomendar la adopción de tecnologías  
44  
45 433 sanitarias en España: evidencias procedentes de una revisión de la literatura.  
46  
47 434 *Pharmacoeconomics Spanish Res Artic*. 2007;4:97–107.  
48  
49  
50  
51 435 20. Briggs AA. Decision Modelling for Health Economic Evaluation. *Handbooks Heal*  
52  
53 436 *Econ Eval Ser*. 2006;2–3.  
54  
55  
56 437 21. Zaidat OO, Ribo M, Mattle HP, Saver JL, Bozorgchami H, Yoo AJ, et al. Health  
57  
58 438 economic impact of first-pass success among patients with acute ischemic stroke  
59  
60

1  
2  
3 439 treated with mechanical thrombectomy: A United States and European perspective. J  
4  
5 440 Neurointerv Surg. 2020;1–7.

6  
7  
8 441 22. Kunz WG, Almekhlafi MA, Menon BK, Saver JL, Hunink MG, Dippel DWJ, et al.  
9  
10 442 Public health and cost benefits of successful reperfusion after thrombectomy for  
11  
12 443 stroke. Stroke. 2020;899–907.

13  
14  
15  
16 444 23. Wu X, Khunte M, Gandhi D, Matouk C, Hughes DR, Sanelli P, et al. Implications of  
17  
18 445 achieving TICI 2b vs TICI 3 reperfusion in patients with ischemic stroke: A cost-  
19  
20 446 effectiveness analysis. J Neurointerv Surg. 2020;12(12):1161–5.

21  
22  
23 447

24  
25  
26 448

27  
28  
29 449 **Figure Legends**

30  
31  
32 450 **Figure 1. mRS outcomes at 90 days Base case and Alternative Scenario.**

33  
34 451 Acronyms: FPE (First Pass Effect); mRS (modified Rankin Score);

35  
36  
37 452 **Figure 2. Tornado diagram of deterministic sensitivity analysis**

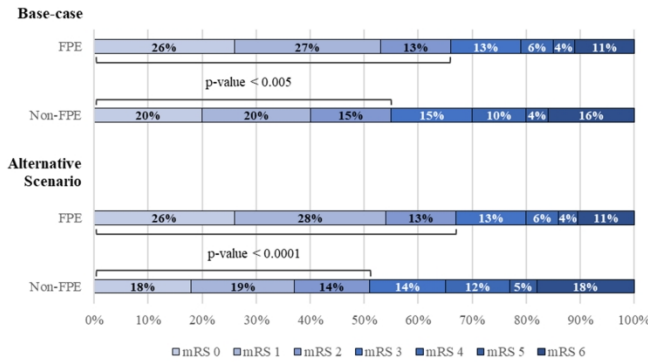
38  
39 453 Acronyms: FPE (First Pass Effect); mRS (modified Rankin Score); RR (Relative Risk)

40  
41 454 **Figure 3. Probabilistic sensitivity analysis**

42  
43 455 Acronyms: QALYs (Quality-Adjusted Life Years).

44  
45  
46 456

1



2

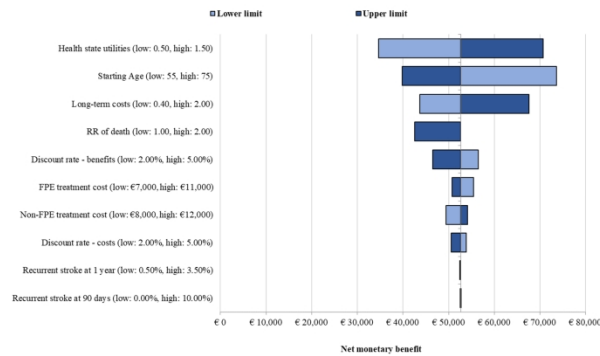


Figure 1 - mRS outcomes at 90 days Base case and Alternative Scenario. Acronyms: FPE (First Pass Effect); mRS (modified Rankin Score). Figure 2 - Tornado diagram of deterministic sensitivity analysis. Acronyms: FPE (First Pass Effect); mRS (modified Rankin Score); RR (Relative Risk)

190x275mm (300 x 300 DPI)



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

3

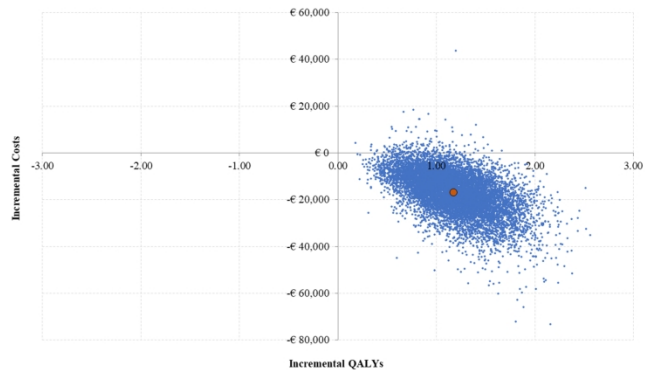


Figure 3 - Probabilistic sensitivity analysis. Acronyms: QALYs (Quality-Adjusted Life Years).  
190x275mm (300 x 300 DPI)

1  
2  
3 **Economic analysis of the first pass effect in mechanical thrombectomy for acute ischemic stroke**  
4 **treatment in Spain.**  
5

6 **Supplementary Material**  
7

8 Eva González-Díaz<sup>1</sup>, MD; Carlos Rodríguez-Paz<sup>2</sup>, MD; Andres Fernandez-Prieto<sup>3</sup>, MD; Mario Martínez-  
9 Galdámez<sup>4</sup>, MD; Rosa Martínez-Moreno<sup>5</sup>, MD; Joaquín Ortega Quintanilla<sup>6</sup>, MD; Alejandro Tomasello<sup>7,8</sup>, MD;  
10 Joaquín Zamarró<sup>9</sup>, MD; David S. Liebeskind, MD<sup>10</sup>; Osama O. Zaidat<sup>11</sup>, MD, MS; Nils H. Mueller-Kronast,  
11 MD<sup>12</sup>.  
12  
13  
14

15 <sup>1</sup> Neurointerventional radiology, Radiology department, Cruces University Hospital, , Barakaldo, Basque  
16 Country, Spain.  
17

18 <sup>2</sup>Neuroradiology Unit, Department of Radiology, Hospital Álvaro Cunqueiro, Vigo, Spain  
19

20 <sup>3</sup>Neurointerventional radiology, Radiology department, Hospital Universitario La Paz, Madrid, Spain.  
21

22 <sup>4</sup>Neuroradiology Unit, University Clinical Hospital of Valladolid, Valladolid, Spain  
23

24 <sup>5</sup>Hospital Universitario Virgen de las Nieves, Granada, Spain.  
25

26 <sup>6</sup>Interventional Neuroradiology, Hospital Universitario Virgen del Rocío, Sevilla, Andalucía, Spain  
27

28 <sup>7</sup> Interventional Neuroradiology Section, Department of Radiology, Vall d'Hebron University Hospital  
29 Barcelona, Spain.  
30

31 <sup>8</sup>Vall d'Hebron Research Institute (VHIR), Vall d'Hebron University Hospital, Barcelona, Spain  
32

33 <sup>9</sup>Interventional Neuroradiology, Hospital Clinico Universitario Virgen de la Arrixaca, Murcia, Spain  
34

35 <sup>10</sup>Neurovascular Imaging Core and UCLA Stroke Center, Department of Neurology, University of California  
36 Los Angeles, Los Angeles, California, USA  
37

38 <sup>11</sup> St Vincent Mercy Hospital, Toledo, Ohio, USA  
39

40 <sup>12</sup> Advanced Neuroscience Network/Tenet South Florida, Delray Beach, Florida, USA  
41

42 **Corresponding author:** Eva Gonzalez-Diaz, [evagonzalezdiaz@yahoo.com](mailto:evagonzalezdiaz@yahoo.com), Neurointerventional Radiology,  
43 Radiology department, Cruces University Hospital, Plaza Cruces S/N 48903, Barakaldo, Basque Country,  
44 Spain, +34669309168  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60**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]**

<b>AIS diagnosis + IV-tPA (tPA 30% of patients)</b>			
<b>Item</b>	<b>Unit cost (€)</b>	<b>Units</b>	<b>Total cost (€)</b>
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
<b>Costs group "FIRST PASS"</b>			
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

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

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
<b>Costs group "Non-FIRST PASS"</b>			
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 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 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
<b>Neurological history</b>			
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
<b>Neurological history</b>			
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**

<b>Patient group</b> <b>Base case</b>	<b>symptomatic intracranial</b> <b>hemorrhage*</b>	<b>malignant cerebral edema</b>
FPE	0.7%	1%
Non-FPE	2.3%	1.4%
P-values are obtained from Fisher's exact test	0.1154	0.7303
<b>Patient group</b> <b>Alternative Scenario</b>	<b>symptomatic intracranial</b> <b>hemorrhage</b>	<b>malignant cerebral edema</b>
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 $\geq$ 4 points worsening on the NIHSS scale within 24 hours.		

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

### 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 Estadística. 2018 Mortality tables of Spanish population. National results. In: INEbase. [Internet]. 2018 [cited 2020 Oct 10]. Available from: [www.ine.es](http://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
<b>Title and abstract</b>			
Title	1	Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared.	<a href="#">Lines 1-2</a>
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.	<a href="#">Lines 44-71</a>
<b>Introduction</b>			
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.	<a href="#">Lines 95-115</a> <a href="#">Lines 117-119</a>
<b>Methods</b>			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	<a href="#">Lines 147-152</a>
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	<a href="#">Line 127</a>
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	<a href="#">Line 127</a> <a href="#">Lines 180-182</a>
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	<a href="#">Lines 126-129</a>
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	<a href="#">Line 129</a>
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	<a href="#">Lines 191-192</a>
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.	<a href="#">Lines 199-202</a>
Measurement of effectiveness	11a	<i>Single study-based estimates:</i> Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	<a href="#">NA</a>



1		11b	<i>Synthesis-based estimates</i> : Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	NA
2				
3				
4	Measurement and	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	NA
5	valuation of preference			
6	based outcomes			
7				
8	Estimating resources	13a	<i>Single study-based economic evaluation</i> : 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
9	and costs			
10				
11				
12				
13				
14				
15		13b	<i>Model-based economic evaluation</i> : 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
16				
17				
18				
19				
20				
21				
22	Currency, price date,	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
23	and conversion			
24				
25				
26				
27				
28	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
29				
30				
31	Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Lines 134-144
32				
33				
34	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
35				
36				
37				
38				
39				
40				
41				
42	<b>Results</b>			
43	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
44				
45				
46				
47				
48	Incremental costs and	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
49	outcomes			
50				
51				
52				
53	Characterising	20a	<i>Single study-based economic evaluation</i> : Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	NA
54	uncertainty			
55				
56				
57				
58				
59				
60				

1		of methodological assumptions (such as discount rate, study perspective).	NA
2			
3			
4	20b	<i>Model-based economic evaluation</i> : 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
5			
6			
7	Characterising heterogeneity	21	
8		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
9			
10			
11			
12			
13	<b>Discussion</b>		
14	Study findings, limitations, generalisability, and current knowledge	22	
15		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
16			
17			
18			
19	<b>Other</b>		
20	Source of funding	23	
21		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
22			
23			
24	Conflicts of interest	24	
25		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
26			
27			
28			
29			

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>

The citation for the CHEERS Task Force Report is:  
 Husereau D, Drummond M, Petrou S, et al. 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. *Value Health* 2013;16:231-50.





# BMJ Open

## 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.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-054816.R1
Article Type:	Original research
Date Submitted by the Author:	17-Dec-2021
Complete List of Authors:	González Diaz, Eva; Cruces University Hospital, Neurointerventional radiology, Radiology department Rodríguez-Paz, Carlos; Hospital Álvaro Cunqueiro, Neuroradiology Unit, Department of Radiology Fernandez-Prieto, Andres; Hospital Universitario La Paz, Neurointerventional radiology, Radiology department Martínez-Galdámez, Mario; University Clinical Hospital of Valladolid, Neuroradiology Unit Martínez-Moreno, Rosa; Hospital Universitario Virgen de las Nieves Ortega Quintanilla, Joaquín; Hospital Universitario Virgen del Rocío Tomasello, Alejandro; Vall d'Hebron University Hospital, Interventional Neuroradiology Section, Department of Radiology; Vall d'Hebron University Hospital, Vall d'Hebron Research Institute (VHIR) Zamarro, Joaquín; Hospital Clínico Universitario Virgen de la Arrixaca, Interventional Neuroradiology Liebeskind, David; University of California Los Angeles, Neurovascular Imaging Core and UCLA Stroke Center, Department of Neurology Zaidat, Osama; St Vincent Mercy Hospital Mueller-Kronast, nils; Advanced Neuroscience Network/Tenet South Florida
<b>Primary Subject Heading</b>:	Health economics
Secondary Subject Heading:	Neurology, Radiology and imaging
Keywords:	HEALTH ECONOMICS, Stroke < NEUROLOGY, Interventional radiology < RADIOLOGY & IMAGING, Neuroradiology < NEUROLOGY

SCHOLARONE™  
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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

4  
5 Eva González-Díaz<sup>1</sup>, MD; Carlos Rodríguez-Paz<sup>2</sup>, MD; Andres Fernandez-Prieto<sup>3</sup>, MD; Mario  
6 Martínez-Galdámez<sup>4</sup>, MD; Rosa Martínez-Moreno<sup>5</sup>, MD; Joaquín Ortega Quintanilla<sup>6</sup>, MD;  
7 Alejandro Tomasello<sup>7,8</sup>, MD; Joaquín Zamarro<sup>9</sup>, MD; David S. Liebeskind, MD<sup>10</sup>; Osama O.  
8 Zaidat<sup>11</sup>, MD, MS; Nils H. Mueller-Kronast, MD<sup>12</sup>.

9  
10  
11  
12 <sup>1</sup>Neurointerventional radiology, Radiology department, Cruces University Hospital, Barakaldo,  
13 Basque Country, Spain.

14 <sup>2</sup>Neuroradiology Unit, Department of Radiology, Hospital Álvaro Cunqueiro, Vigo, Spain

15 <sup>3</sup>Neurointerventional radiology, Radiology department, Hospital Universitario La Paz, Madrid,  
16 Spain.

17 <sup>4</sup>Neuroradiology Unit, University Clinical Hospital of Valladolid, Valladolid, Spain

18 <sup>5</sup>Hospital Universitario Virgen de las Nieves, Granada, Spain.

19 <sup>6</sup>Interventional Neuroradiology, Hospital Universitario Virgen del Rocío, Sevilla, Andalucía,  
20 Spain

21 <sup>7</sup>Interventional Neuroradiology Section, Department of Radiology, Vall d'Hebron University  
22 Hospital, Barcelona, Spain.

23 <sup>8</sup>Vall d'Hebron Research Institute (VHIR), Vall d'Hebron University Hospital, Barcelona,  
24 Spain

1  
2  
3 25 <sup>9</sup> Interventional Neuroradiology, Hospital Clinico Universitario Virgen de la Arrixaca, Murcia,  
4  
5 26 Spain

6  
7  
8 27 <sup>10</sup> Neurovascular Imaging Core and UCLA Stroke Center, Department of Neurology,  
9  
10 28 University of California Los Angeles, Los Angeles, California, USA

11  
12 29 <sup>11</sup> St Vincent Mercy Hospital, Toledo, Ohio, USA

13  
14 30 <sup>12</sup> Advanced Neuroscience Network/Tenet South Florida, Delray Beach, Florida, USA

15  
16  
17 31

18  
19 32

20  
21 33

22  
23  
24 34 **Corresponding author:** Eva González-Díaz, [evagonzalezdiaz@yahoo.com](mailto:evagonzalezdiaz@yahoo.com),  
25  
26 35 Neurointerventional Radiology, Radiology department, Cruces University Hospital, Plaza  
27  
28 36 Cruces S/N 48903, Barakaldo, Basque Country, Spain, +34669309168

29  
30  
31 37

32  
33 38

34  
35 39

36  
37  
38 40 **Keywords:** First-pass effect, health economics, ischaemic stroke, mechanical thrombectomy,  
39  
40 41 net monetary benefit, reperfusion, Spain

41  
42 42 **Word count:** 2,773

43  
44 43 **Total number of tables and figures:** 2 Tables, 3 Figures

45  
46  
47 44

1  
2  
3 **Abstract**  
4

5 **Objective:** The mechanical thrombectomy (MT) benefit is related to the degree of reperfusion  
6  
7 achieved. First Pass Effect (FPE) is defined as complete/near revascularization of the large  
8  
9 vessel occlusion (modified Thrombolysis in Cerebral Infarction (mTICI) 2c-3) after a single  
10  
11 device pass. This study assessed the health benefit and economic impact of achieving FPE for  
12  
13 acute ischemic stroke (AIS) patients from the Spanish National Health System (NHS)  
14  
15 perspective.  
16  
17

18  
19 **Design:** A lifetime Markov model was used to estimate incremental costs and health outcomes  
20  
21 (measured in quality-adjusted life-years [QALY]) of patients that achieve FPE. A sub-analysis  
22  
23 of the STRATIS registry was performed to obtain clinical outcomes. The base-case included  
24  
25 all patients that achieved at least a final mTICI $\geq$ 2b, while the alternative scenario included all  
26  
27 patients regardless of their final mTICI (0-3). Treatment costs were updated to reflect current  
28  
29 practice based on expert panel consensus, while other acute and long-term costs were obtained  
30  
31 from a previous cost-effectiveness analysis of MT performed in Spain. Sensitivity analyses  
32  
33 were performed to assess the model's robustness.  
34  
35

36  
37 **Setting:** Spanish healthcare perspective.  
38

39  
40 **Participants:** AIS patients in Spain.  
41

42  
43 **Interventions:** FPE following MT.  
44

45  
46 **Outcome measures:** The model estimated QALYs, lifetime costs and net monetary benefit  
47  
48 (NMB) for the FPE and non-FPE group, depending on the inclusion of reperfusion groups and  
49  
50 formal care costs.  
51

52  
53 **Results:** STRATIS sub-analysis estimated significantly better clinical outcomes at 90-days for  
54  
55 the FPE group in all scenarios. In the base-case, the model estimated lifetime cost-saving per  
56  
57 patient of €16,583 and an incremental QALY gain of 1.2 years of perfect health for the FPE  
58  
59  
60

69 group. Cost-savings and QALY gains were greater in the alternative scenario (-€44,289; 1.75).

70 In all scenarios, cost-savings were driven by the long-term cost reduction.

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

73

74

## 75 **Article Summary**

76 Strengths and limitations of this study

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

86

87

88

89

90

91

92

93

## 94 INTRODUCTION

95

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

102

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

109

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

117

1  
2  
3 118 The objective of this study is to assess the health outcome benefits and economic impact of  
4  
5 119 achieving FPE for the AIS patients from the National Health System (NHS) perspective in  
6  
7  
8 120 Spain.

9  
10 121

11  
12 122

13  
14 123

## 15 16 17 124 **METHODS**

18  
19 125

### 20 21 126 **Model structure**

22  
23  
24 127 A previously published cost-effectiveness model comparing MT + IV-tPA with IV-tPA alone  
25  
26 128 in a Spanish NHS setting was modified to reflect only patients that received MT treatment  
27  
28 129 which afterwards were stratified to reflect those who achieved FPE and those who didn't (Non-  
29  
30 130 FPE) (5), and allowed to estimate lifetime health and costs outcomes of the two patient groups.  
31  
32  
33 131 As in the previous modelling, this analysis is also over the patient's lifetime and from the  
34  
35 132 Spanish NHS perspective. The model was developed using Microsoft Excel (Microsoft  
36  
37 133 Corporation, Redmond, WA, USA).

38  
39  
40 134

41  
42 135 The model had a two-phase structure, consisting of an acute-subacute phase from stroke onset  
43  
44 136 to 90 days, and a rest-of-life phase 91 days after stroke to the end of patient's life. In the acute-  
45  
46 137 subacute phase, patients enter the model once reperfusion status (FPE vs Non-FPE) has been  
47  
48 138 determined, and then are assigned to one of the seven mutually exclusive health states based  
49  
50 139 on Modified Ranking Scale (mRS; 0-no symptoms, 6-death) to reflect several degrees of  
51  
52 140 disability at 90 days. Afterwards, patients enter a Markov structure, from 91 days after the  
53  
54 141 stroke to the end of the patients' life. In this phase, patients could remain in the same health  
55  
56 142 state or transition to different states during each annual cycle until the end of life, depending  
57  
58  
59  
60



1  
2  
3 143 on the occurrence of a recurrent stroke or death from other causes (age-gender specific  
4  
5 144 mortality). A half-cycle correction was used to account for transitions occurring in the middle  
6  
7  
8 145 of a cycle.  
9

10 146

### 11 12 147 **Patient population**

13  
14 148 The model simulates a hypothetical cohort of 1,000 patients with clinic-demographic  
15  
16 149 characteristics based on the STRATIS registry (Systematic Evaluation of Patients Treated With  
17  
18 150 Neurothrombectomy Devices for Acute Ischemic Stroke) (12). STRATIS registry patients  
19  
20 151 were classified into 2 groups: patients with a final mTICI  $\geq 2b$  (used for the base case analysis),  
21  
22 152 and patients with final mTICI (0-3) (used for the alternative scenario). Afterwards, patients in  
23  
24 153 both groups were stratified into FPE and non-FPE groups.  
25  
26  
27

28 154

### 29 30 155 **Clinical data**

31  
32 156 Clinical data was obtained from a sub-analysis of the STRATIS registry (12) in which FPE and  
33  
34 157 Non-FPE groups were compared. Moreover, it was considered that patients were at risk of  
35  
36 158 experiencing adverse events (symptomatic intracranial hemorrhage and malignant cerebral  
37  
38 159 edema) during the acute-subacute phase, therefore adverse events data was also obtained from  
39  
40 160 STRATIS registry sub-analysis.  
41  
42  
43

44 161

45  
46 162 Categorical variables were compared using  $\chi^2$  (Chi-square) test and Mantel-Haenszel Chi-  
47  
48 163 square test when appropriate. Proportion differences were compared by z-test both one-sided  
49  
50 164 and two-sided tests are performed (considering 5% and 2.5% significance level respectively).  
51  
52 165 All statistical analyses were performed using SAS version 9.4.  
53  
54  
55

56 166  
57  
58  
59  
60

1  
2  
3 167 Background age-gender related mortality was obtained from the latest available Life Table in  
4  
5 168 Spain (data from 2018) (13) and relative risks of death by mRS score were used to adjust age-  
6  
7  
8 169 gender-related mortality (14) to account for the increased risks observed among stroke  
9  
10 170 survivors (Supplementary Material Table A1 & A2). Recurrence stroke rates were obtained  
11  
12 171 from Mohan et al. (15) (Supplementary Material (Table A3).

172

### 173 **Quality of life**

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

179

### 180 **Costs**

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

188

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

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

194

195 **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		

196

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

198

### 199 **Economic model outcomes and sensitivity analysis**

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

204

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

1  
2  
3 210 parameters simultaneously (mRS scores at 90 days (Dirichlet), mortality relative risks  
4  
5 211 (Lognormal), starting age (Normal), utilities (Beta) and costs (Gamma)), to account for the  
6  
7  
8 212 general uncertainty around model inputs (5).  
9

10 213

## 11 214 **Patient and public involvement**

12  
13  
14 215 This study was conducted without patient and public involvement. Therefore, patients were not  
15  
16  
17 216 involved in the study design, reporting or interpretation of the findings. This study included a  
18  
19 217 post-hoc analysis of an existing study, therefore institutional review board approval was not  
20  
21 218 obtained for this analysis. Moreover, no research approval was required for model input  
22  
23  
24 219 parameters that were obtained from literature or based on panel of experts consensus.  
25

26 220

27 221

28 222

## 29 223 **RESULTS**

30 224

31  
32  
33 225 Based on STRATIS sub-analysis, the mean age of stroke considered in the model was 68 years.  
34  
35 226 Both groups have similar characteristics at baseline. Descriptive statistics on the FPE and Non-  
36  
37 227 FPE groups are reported in Supplementary Material, Tables A6-A7-A8-A9.  
38  
39

40 228

41  
42  
43 229 Our results suggest that the FPE group had significantly better clinical outcomes at 90 days  
44  
45 230 after stroke compared to the Non-FPE group in the base-case scenario (mRS 0-2: 66.2% vs  
46  
47 231 54.6%, p-value<0.005). Similar results in the alternative scenario were observed (mRS 0-2:  
48  
49 232 66.9% vs 50.6%, p-value<0.0001) (Figure 1). Adverse events results across scenario  
50  
51 233 populations are presented in the Supplementary Material (Table A10).  
52  
53

54 234

**[Insert Figure 1]**

1  
2  
3 235 In the base-case scenario, the model estimates an average lifetime cost per patient equal to  
4  
5 236 €97,206 for the FPE group and €113,790 for the Non-FPE group. Of these, 83% were  
6  
7 237 associated with long-term costs. Overall, the FPE group generated a cost reduction of €16,583  
8  
9 238 per patient in a lifetime horizon. Cost reductions are predicted to be greater when  
10  
11 239 nursing/residential care cost are included, leading to a savings of €30,072 per patient.  
12  
13  
14  
15

240

16  
17 241 In terms of health outcomes, the model estimates that achieving FPE lead to a QALY gain of  
18  
19 242 1.2 years (7.89 vs 6.69), while the number of independent people at 90 days is also projected  
20  
21 243 to increase by 116 (662 vs 546) in this hypothetical cohort. However, there is an estimated  
22  
23 244 increase in the total number of recurrent strokes in the FPE group due to patients living longer  
24  
25 245 (283 vs 257).  
26  
27  
28

246

29  
30 247 The model suggests that achieving FPE lead to a NMB of €52,634 considering a WTP of  
31  
32 248 €30,000/QALY gained. The NMB was expected to increase to €66,122 when  
33  
34 249 nursing/residential care cost are considered. FPE provides greater net economic value  
35  
36 250 demonstrating higher efficacy with lower costs from the payer perspective in a lifetime time  
37  
38 251 horizon (Table 2). In the alternative scenario, similar results were observed, which may confirm  
39  
40 252 the greater benefits that achieving FPE (between 32%-47% higher) may provide when all  
41  
42 253 patients regardless their final mTICI are considered (QALY gain of 1.75 years and €21,910  
43  
44 254 cost reduction; when considering nursing/residential costs, a cost reduction of €44,289 and a  
45  
46 255 NMB of €96,684) (Table 2).  
47  
48  
49  
50

256

257

258

259

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

Costs	Base-case			Alternative scenario		
	FPE	Non-FPE	Incremental	FPE	Non-FPE	Incremental
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
<b>Total costs (€)</b>	<b>97,206</b>	<b>113,790</b>	<b>-16,583</b>	<b>95,925</b>	<b>117,836</b>	<b>-21,910</b>
NMB (€)			52,634			74,306
<b>Total costs (With nursing/residential care cost) (€)</b>	<b>161,982</b>	<b>192,054</b>	<b>-30,072</b>	<b>159,565</b>	<b>203,854</b>	<b>-44,289</b>
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

261

262

263 **Sensitivity analysis**

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

271

**[Insert Figure 2]**

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

272

**[Insert Figure 3]**

273

274

For peer review only

1  
2  
3 275 **DISCUSSION**  
4

5 276  
6

7  
8 277 Clinical evidence suggests that achieving FPE after a single pass is associated with favourable  
9  
10 278 outcomes after a MT procedure (6,7). Our study estimated the health gains from achieving FPE  
11  
12 279 and examined the associated economic impact from the Spanish NHS perspective over a  
13  
14 280 lifetime horizon.  
15

16  
17 281

18  
19 282 Clinical outcomes, based on a sub-analysis from the STRATIS registry, showed that achieving  
20  
21 283 mTICI 2c-3 reperfusion after a single pass leads to significantly better overall mRS distribution  
22  
23 284 and functional independence (mRS 0-2). The difference in the proportion in mRS 0-2 between  
24  
25 285 FPE and Non-FPE groups ranged between 11.5% to 16.3% depending on the cohort of patients  
26  
27 286 (Figure 1). Similar findings have been described in literature (8)(21)(22). An analysis of North  
28  
29 287 American Solitaire Acute Stroke Registry conducted by Zaidat et al. suggested that if patients  
30  
31 288 achieved mTICI 3, the FPE lead to better clinical outcomes compared to the rest of the cohort  
32  
33 289 that did not achieve FPE (61.3% vs 35.3%, p-value: <0.0001) (8). The meta-analysis by Abbasi  
34  
35 290 et al. reported on the association between FPE and clinical outcomes finding higher rates of  
36  
37 291 functional independence for FPE compared to Non-FPE (56% vs 41%, p-value: <0.01) and  
38  
39 292 lower mortality (17% vs 25%, p-value: <0.01) (21). Furthermore, a recent meta-analysis that  
40  
41 293 conducted a per-pass analysis of recanalization and health outcomes in thrombectomy (22)  
42  
43 294 suggests that the likelihood of functional independence in patients with final successful  
44  
45 295 recanalization decreased after each pass. On the first pass, 55% of patients achieved mRS 0-2  
46  
47 296 (p-value: 0.033), while rates progressive declined after each subsequent pass, dropping to 26%  
48  
49 297 for patients who required 5 or more passes for successful recanalization. The results of our  
50  
51 298 analysis also confirm improved health outcomes from achieving FPE and are therefore  
52  
53 299 coherent with existing literature.  
54  
55  
56  
57  
58  
59  
60



1  
2  
3 300  
4

5 301 The base-case results suggest that achieving FPE yields better health outcomes than Non-FPE  
6  
7 302 group, providing an incremental QALY gain of 1.2, equivalent to 438 days in perfect health.

8  
9  
10 303 From the cost perspective, the FPE group is associated with lower health care costs, leading to  
11  
12 304 a cost-saving of €16,583 and €30,072 when considering nursing/residential healthcare costs

13  
14 305 (Table 2). QALYs and cost-savings resulted to be greater in the alternative scenario: the FPE

15  
16 306 group lead to 1.75 additional QALYs per patient (or 657 days in full health) and €21,910 in

17  
18 307 savings (€44,289 when considering nursing/residential healthcare costs). The greater results

19  
20 308 observed in the alternative scenario can be explained by a slight increase in good functional

21  
22 309 outcomes in the FPE group, accompanied by a decrease in the mRS 0-2 in the non-FPE group,

23  
24 310 which contributed to an even larger incremental difference between FPE and non-FPE

25  
26 311 outcomes in this scenario.

27  
28 312 Cost savings in both scenarios were mainly driven by reductions in long-term costs associated

29  
30 313 with the management of functionally dependent patients. Furthermore, all results were tested

31  
32 314 by performing DSA and PSA which demonstrated that our results are robust. In both scenarios

33  
34 315 and sub-scenarios, the Non-FPE group was associated with lower health benefits and higher

35  
36 316 health care costs.

37  
38 317

39  
40 318 Improved health outcomes are generally associated with economic benefits. Even though there

41  
42 319 is less literature available on cost-implications from FPE, a recently published study (23)

43  
44 320 estimated the short-term cost implications of FPE in several countries, including Spain. The

45  
46 321 authors estimated the procedural/hospitalization and annual care costs differences considering

47  
48 322 a 1-year time horizon. Similar to our work, the study showed lower procedural/hospitalization

49  
50 323 and annual care costs for patients that achieved FPE vs. Non-FPE across countries considered.

51  
52 324 Furthermore, our findings are compatible with other studies undertaken in the United States

53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 325 that have demonstrated that achieving TICI 3 lead to healthcare and societal cost savings  
4  
5 326 relative to achieving TICI 2b for LVO (24,25).  
6  
7  
8 327

9  
10 328 Overall, the results of this study showed that raising the FPE rate will not only increase the  
11  
12 329 quality of life for patients, but also decrease the overall health care costs. Achieving FPE can  
13  
14 330 potentially be one of the primary goals in the treatment of patients with ischemic stroke due to  
15  
16 331 LVO from both a clinical and economic perspective. Because this analysis was performed from  
17  
18 332 the Spanish NHS perspective, only the direct costs are considered. There could be larger  
19  
20 333 savings associated with achieving FPE if indirect costs, such as informal care and productivity  
21  
22 334 losses, were included.  
23  
24  
25

26 335  
27  
28 336 To our knowledge, this is one of the first studies that aim to evaluate the lifetime health and  
29  
30 337 cost implications of achieving FPE in AIS patients in Spain from the NHS perspective. Among  
31  
32 338 the strengths of this study are the Markov structure (allows to better reflect the patient pathway  
33  
34 339 in terms of lifetime costs and benefits) and the inclusion of comprehensive diagnostics and  
35  
36 340 treatments costs, main adverse events management, and recurrent strokes, to account for all  
37  
38 341 health outcomes and associated costs after a stroke.  
39  
40  
41

42 342  
43  
44 343 This study has some limitations. First, clinical efficacy and patient characteristics were based  
45  
46 344 on the STRATIS registry, which included centers outside Spain. Moreover, the study's reliance  
47  
48 345 on observational data may limit the result's interpretation due to the potential effect that  
49  
50 346 unmeasured confounders (e.g., quality of stroke care, procedural technique) could have on the  
51  
52 347 mRS score variation between groups. Furthermore, the STRATIS registry is based on specific  
53  
54 348 stent retrievers and might not be applicable to other types of devices with different safety and  
55  
56 349 efficacy profile. Also, the average age for a stroke onset in Spain might be higher than our  
57  
58  
59  
60

1  
2  
3 350 assumption for all patients (68 years), which could potentially lead to an overestimation of  
4  
5 351 health outcomes. However, age was included in the DSA, varied to an upper limit of 81 years,  
6  
7 352 and this did not lead to dramatic changes in the results as the NMB remained positive in all  
8  
9  
10 353 scenarios. Third, patients were assumed to remain in a given mRS score until they experienced  
11  
12 354 a recurrent stroke or death. Other factors that may have an effect on mRS scores, such as  
13  
14 355 comorbidities, were not included. However, this aspect could affect both patient cohorts  
15  
16 356 equally considering there are no differences in the baseline characteristics, nonetheless further  
17  
18 357 studies on mRS decline in the long term are encouraged. Acute and long-term costs were  
19  
20 358 obtained from the original cost-effectiveness model and the same limitations for costs would  
21  
22 359 apply. Finally, resource consumption was based on a panel of experts' consensus and clinical  
23  
24 360 practice and subject to heterogeneity between centres. However, these assumptions were tested  
25  
26 361 in the DSA and PSA and did not alter the overall results.  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37

## 364 **CONCLUSION**

38 365 Achieving FPE after MT can lead to important health care cost-saving and better functional  
39  
40 366 clinical outcomes per patient compared to not achieving FPE. Costs saving to the Spanish NHS  
41  
42 367 ranged from -€16,583 to -€44,289 depending on the patient cohort and long-term costs.  
43  
44 368 Increasing FPE rates will lead to greater cost savings to the health care system.  
45  
46  
47  
48  
49  
50  
51

## 52 371 **Acknowledgements**

53  
54 372 The authors acknowledge Medtronic and Valeska Seguel Ravest for its support and editorial  
55  
56 373 assistance.  
57  
58  
59  
60

1  
2  
3 375 **Funding:** This study was sponsored by Medtronic. There is no grant number available for this  
4  
5 376 study.  
6

7  
8 377

9  
10 378 **Competing interests:** EGD, CRP, AFP, RMM, JOQ, JZ declare no conflicts of interest. MMG  
11  
12 379 is a proctor and consultant of Medtronic. AT is a consultant, proctor and advisor of Medtronic  
13  
14 380 (Consultancy Anaconda, Balt, Stryker and Perflow). NHMK is a scientific consultant regarding  
15  
16 381 trial design and conduct for Medtronic. OOO is a consultant for Neuravi/Cerenovus, Stryker,  
17  
18 382 Penumbra, and Medtronic. DSL is an imaging core laboratory consultant for Cerenovus,  
19  
20 383 Genentech, Medtronic, and Stryker.  
21  
22  
23

24 384

25  
26 385 **Contributors:** EGD, CRP, AFP, RMM, JOQ, JZ, AT and MMG: contributed to the design,  
27  
28 386 data collection, analysis, interpretation and drafting, reviewing, and revising the manuscript.  
29  
30 387 NHMK, OOO and DSL: reviewing and revising the manuscript  
31  
32

33 388

34  
35 389 **Patient consent for publication:** Not required.  
36  
37

38 390

39  
40 391 **Data Sharing Statement:** All relevant model inputs used in this study are included in the  
41  
42 392 article and supplement.  
43  
44

45 393

46  
47 394 **Ethics approval:** This study is a post-hoc analysis of an existing study therefore institutional  
48  
49 395 review board approval was not obtained for this analysis.  
50

51 396

52  
53 397

## 54 398 **References**

55  
56  
57  
58 399 1. Stevens, Eleanor; Emmett, Eva; Wang, Yanzhong; McKevitt, Christopher; Wolfe C.  
59  
60

- 1  
2  
3 400 The burden of stroke in Europe report. Stroke Alliance Eur. 2017;131 p.  
4  
5  
6 401 2. Luengo-Fernandez R, Violato M, Candio P, Leal J. Economic burden of stroke across  
7  
8 402 Europe: A population-based cost analysis. Eur Stroke J. 2020;5(1):17–25.  
9  
10  
11 403 3. Turc G, Bhogal P, Fischer U, Khatri P, Lobotesis K, Mazighi M, et al. European  
12  
13 404 Stroke Organisation (ESO) – European Society for Minimally Invasive Neurological  
14  
15 405 Therapy (ESMINT) Guidelines on Mechanical Thrombectomy in Acute Ischaemic  
16  
17 406 Stroke Endorsed by Stroke Alliance for Europe (SAFE). Eur Stroke J. 2019;4(1):6–12.  
18  
19  
20  
21 407 4. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et  
22  
23 408 al. 2018 Guidelines for the Early Management of Patients With Acute Ischemic  
24  
25 409 Stroke: A Guideline for Healthcare Professionals From the American Heart  
26  
27 410 Association/American Stroke Association. Vol. 49, Stroke. 2018. 46–110 p.  
28  
29  
30  
31 411 5. de Andrés-Nogales F, Álvarez M, de Miquel MÁ, Segura T, Gil A, Cardona P, et al.  
32  
33 412 Cost-effectiveness of mechanical thrombectomy using stent retriever after intravenous  
34  
35 413 tissue plasminogen activator compared with intravenous tissue plasminogen activator  
36  
37 414 alone in the treatment of acute ischaemic stroke due to large vessel occlusion in Spa.  
38  
39 415 Eur Stroke J. 2017;2(3):272–84.  
40  
41  
42  
43 416 6. Bai Y, Pu J, Wang H, Yang D, Hao Y, Xu H, et al. Impact of Retriever Passes on  
44  
45 417 Efficacy and Safety Outcomes of Acute Ischemic Stroke Treated with Mechanical  
46  
47 418 Thrombectomy. Cardiovasc Intervent Radiol. 2018;41(12):1909–16.  
48  
49  
50  
51 419 7. Bai X, Zhang X, Yang W, Zhang Y, Wang T, Xu R, et al. Influence of first-pass effect  
52  
53 420 on recanalization outcomes in the era of mechanical thrombectomy: a systemic review  
54  
55 421 and meta-analysis. Neuroradiology. 2020;(77).  
56  
57  
58 422 8. Zaidat OO, Castonguay AC, Linfante I, Gupta R, Martin CO, Holloway WE, et al.  
59  
60

- 1  
2  
3 423 First pass effect: A new measure for stroke thrombectomy devices. *Stroke*.  
4  
5 424 2018;49(3):660–6.  
6  
7  
8 425 9. Zaidat OO, Haussen DC, Hassan AE, Jadhav AP, Mehta BP, Mokin M, et al. Impact of  
9  
10 426 Stent Retriever Size on Clinical and Angiographic Outcomes in the STRATIS Stroke  
11  
12 427 Thrombectomy Registry. *Stroke*. 2019;50(2):441–7.  
13  
14  
15  
16 428 10. Nguyen TN, Malisch T, Castonguay AC, Gupta R, Sun CHJ, Martin CO, et al. Balloon  
17  
18 429 guide catheter improves revascularization and clinical outcomes with the solitaire  
19  
20 430 device : Analysis of the north american solitaire acute stroke registry. *Stroke*.  
21  
22 431 2014;45(1):141–5.  
23  
24  
25  
26 432 11. Di Maria F, Kyheng M, Consoli A, Desilles JP, Gory B, Richard S, et al. Identifying  
27  
28 433 the predictors of first-pass effect and its influence on clinical outcome in the setting of  
29  
30 434 endovascular thrombectomy for acute ischemic stroke: Results from a multicentric  
31  
32 435 prospective registry. *Int J Stroke*. 2020;16(1):20–8.  
33  
34  
35  
36 436 12. Mueller-Kronast NH, Zaidat OO, Froehler MT, Jahan R, et al. Systematic Evaluation  
37  
38 437 of Patients Treated With Neurothrombectomy Devices for Acute Ischemic Stroke:  
39  
40 438 Primary Results of the STRATIS Registry. *Stroke*. 2017;48(10):2760–8.  
41  
42  
43  
44 439 13. Instituto Nacional de Estadística. 2018 Mortality tables of Spanish population.  
45  
46 440 National results. In: INEbase. [Internet]. 2018 [cited 2020 Oct 10]. Available from:  
47  
48 441 [www.ine.es](http://www.ine.es)  
49  
50  
51 442 14. Slot KB, Berge E, Sandercock P, Lewis SC, Dorman P, Dennis M. Causes of death by  
52  
53 443 level of dependency at 6 months after ischemic stroke in 3 large cohorts. *Stroke*.  
54  
55 444 2009;40(5):1585–9.  
56  
57  
58 445 15. Mohan KM, Wolfe CDA, Rudd AG, Heuschmann PU, Kolominsky-Rabas PL, Grieve  
59  
60

- 1  
2  
3 446 AP. Risk and cumulative risk of stroke recurrence: A systematic review and meta-  
4  
5 447 analysis. *Stroke*. 2011;42(5):1489–94.  
6  
7  
8 448 16. Rivero-Arias O, Ouellet M, Gray A, Wolstenholme J, Rothwell PM, Luengo-  
9  
10 449 Fernandez R. Mapping the modified rankin scale (mRS) measurement into the generic  
11  
12 450 EuroQol (EQ-5D) health outcome. *Med Decis Mak*. 2010;30(3):341–54.  
13  
14  
15  
16 451 17. López Bastida J, Oliva J, Antoñanzas F, García-Altés A, Gisbert R, Mar J, et al.  
17  
18 452 Propuesta de guía para la evaluación económica aplicada a las tecnologías sanitarias.  
19  
20 453 *Gac Sanit*. 2010;24(2):154–70.  
21  
22  
23 454 18. Sacristán JA, Oliva J, Del Llano J, Prieto L, Pintod JL. Qué es una tecnología  
24  
25 455 sanitaria eficiente en España? *Gac Sanit*. 2002;16(4):334–43.  
26  
27  
28  
29 456 19. De Cock E, Miravittles EM, González-Juanatey JR, Azanza-Perea JR. Valor umbral  
30  
31 457 del coste por año de vida ganado para recomendar la adopción de tecnologías  
32  
33 458 sanitarias en España: evidencias procedentes de una revisión de la literatura.  
34  
35 459 *PharmacoEconomics Spanish Res Artic*. 2007;4:97–107.  
36  
37  
38  
39 460 20. Briggs AA. *Decision Modelling for Health Economic Evaluation*. Handbooks Heal  
40  
41 461 *Econ Eval Ser*. 2006;2–3.  
42  
43  
44 462 21. Abbasi M, Liu Y, Fitzgerald S, Mereuta OM, Larco JLA, Rizvi A, et al. Systematic  
45  
46 463 review and meta-analysis of current rates of the first-pass effect by thrombectomy  
47  
48 464 technique and associations with clinical outcomes. *J Neurointervent Surg*. 2021; 13:  
49  
50 465 212-216.  
51  
52  
53 466 22. Larco JA, Abbasi M, Liu Y, Madhani SI, Shahid AH, Kadirvel R, et al. Per-pass  
54  
55 467 analysis of recanalization and good neurological outcome in thrombectomy for stroke:  
56  
57 468 Systematic review and meta-analysis. *Interventional Neuroradiology*. 2021.  
58  
59  
60

- 1  
2  
3 469 23. Zaidat OO, Ribo M, Mattle HP, Saver JL, Bozorgchami H, Yoo AJ, et al. Health  
4  
5 470 economic impact of first-pass success among patients with acute ischemic stroke  
6  
7 471 treated with mechanical thrombectomy: A United States and European perspective. J  
8  
9 472 Neurointerv Surg. 2020;1–7.
- 10  
11  
12  
13 473 24. Kunz WG, Almekhlafi MA, Menon BK, Saver JL, Hunink MG, Dippel DWJ, et al.  
14  
15 474 Public health and cost benefits of successful reperfusion after thrombectomy for  
16  
17 475 stroke. Stroke. 2020;899–907.
- 18  
19  
20 476 25. Wu X, Khunte M, Gandhi D, Matouk C, Hughes DR, Sanelli P, et al. Implications of  
21  
22 477 achieving TICI 2b vs TICI 3 reperfusion in patients with ischemic stroke: A cost-  
23  
24 478 effectiveness analysis. J Neurointerv Surg. 2020;12(12):1161–5.

479

480

## 481 **Figure Legends**

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

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

### 484 **Figure 2. Tornado diagram of deterministic sensitivity analysis**

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

### 486 **Figure 3. Probabilistic sensitivity analysis**

487 Acronyms: QALYs (Quality-Adjusted Life Years).

488



1

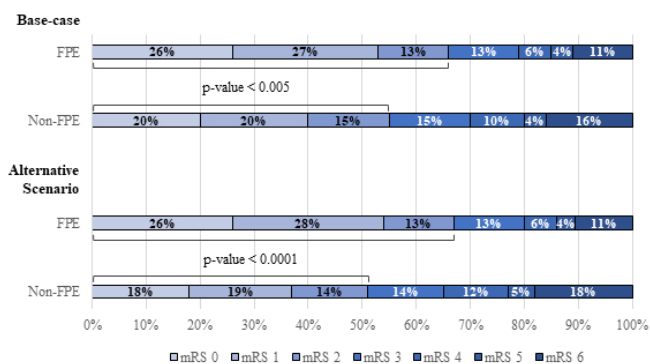


Figure 1 - mRS outcomes at 90 days Base case and Alternative Scenario. Acronyms: FPE (First Pass Effect); mRS (modified Rankin Score).

190x275mm (96 x 96 DPI)

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

2

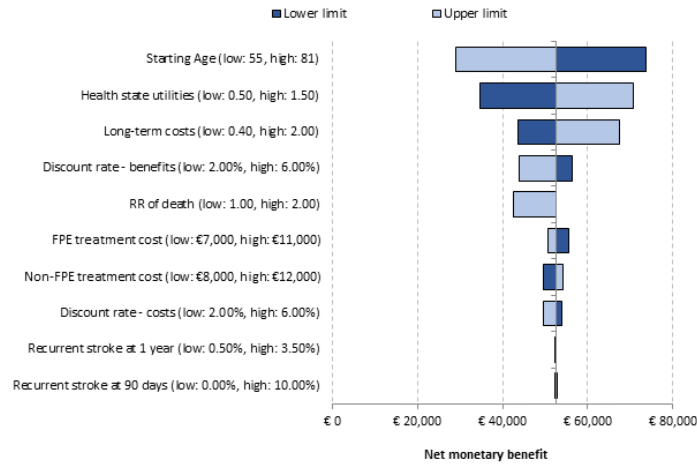


Figure 2 - Tornado diagram of deterministic sensitivity analysis. Acronyms: FPE (First Pass Effect); mRS (modified Rankin Score); RR (Relative Risk)

190x275mm (96 x 96 DPI)

3

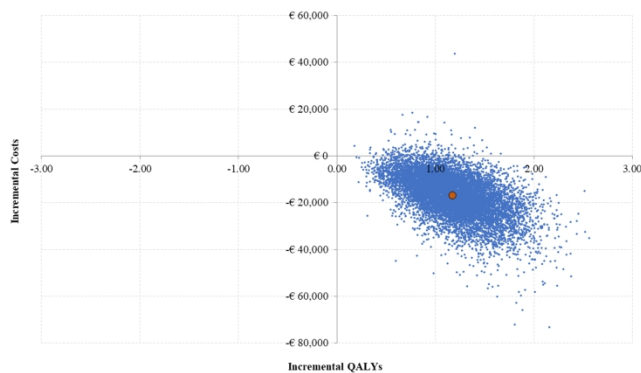


Figure 3 - Probabilistic sensitivity analysis. Acronyms: QALYs (Quality-Adjusted Life Years).

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]**

<b>AIS diagnosis + IV-tPA (tPA 30% of patients)</b>			
<b>Item</b>	<b>Unit cost (€)</b>	<b>Units</b>	<b>Total cost (€)</b>
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
<b>Costs group "FIRST PASS"</b>			
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

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

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
<b>Costs group "Non-FIRST PASS"</b>			
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 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 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
<b>Neurological history</b>			
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
<b>Neurological history</b>			
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**

<b>Patient group Base case</b>	<b>symptomatic intracranial hemorrhage*</b>	<b>malignant cerebral edema</b>
FPE	0.7%	1%
Non-FPE	2.3%	1.4%
P-values are obtained from Fisher's exact test	0.1154	0.7303
<b>Patient group Alternative Scenario</b>	<b>symptomatic intracranial hemorrhage</b>	<b>malignant cerebral edema</b>
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 $\geq$ 4 points worsening on the NIHSS scale within 24 hours.		

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

### 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 Estadística. 2018 Mortality tables of Spanish population. National results. In: INEbase. [Internet]. 2018 [cited 2020 Oct 10]. Available from: [www.ine.es](http://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
<b>Title and abstract</b>			
Title	1	Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared.	<a href="#">Lines 1-2</a>
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.	<a href="#">Lines 44-71</a>
<b>Introduction</b>			
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.	<a href="#">Lines 95-115</a> <a href="#">Lines 117-119</a>
<b>Methods</b>			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	<a href="#">Lines 147-153</a>
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	<a href="#">Line 128</a>
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	<a href="#">Line 128</a> <a href="#">Lines 180-182</a>
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	<a href="#">Lines 126-130</a>
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	<a href="#">Line 130</a>
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	<a href="#">Lines 191-193</a>
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.	<a href="#">Lines 199-202</a>
Measurement of effectiveness	11a	<i>Single study-based estimates:</i> Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	<a href="#">NA</a>



1		11b	<i>Synthesis-based estimates</i> : Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	NA
2				
3				
4				
5	Measurement and	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	NA
6	valuation of preference			
7	based outcomes			
8	Estimating resources	13a	<i>Single study-based economic evaluation</i> : 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
9	and costs			
10				
11				
12				
13				
14				
15		13b	<i>Model-based economic evaluation</i> : 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
16				
17				
18				
19				
20				
21				
22	Currency, price date,	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
23	and conversion			
24				
25				
26				
27				
28	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
29				
30				
31	Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Lines 134-144
32				
33				
34	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
35				
36				
37				
38				
39				
40				
41				
42	<b>Results</b>			
43	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
44				
45				
46				
47				
48				
49	Incremental costs and	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
50	outcomes			
51				
52				
53	Characterising	20a	<i>Single study-based economic evaluation</i> : Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	NA
54	uncertainty			
55				
56				
57				
58				
59				
60				



1		of methodological assumptions (such as discount rate, study perspective).	NA
2			
3			
4	20b	<i>Model-based economic evaluation</i> : 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
5			
6			
7	Characterising heterogeneity	21	
8		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
9			
10			
11			
12			
13	<b>Discussion</b>		
14	Study findings, limitations, generalisability, and current knowledge	22	
15		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
16			
17			
18			
19	<b>Other</b>		
20	Source of funding	23	
21		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
22			
23			
24	Conflicts of interest	24	
25		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
26			
27			
28			
29			

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>

The citation for the CHEERS Task Force Report is:  
 Husereau D, Drummond M, Petrou S, et al. 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. *Value Health* 2013;16:231-50.

