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# Health economic impact of first-pass success among patients with acute ischemic stroke treated with mechanical thrombectomy: a United States and European perspective

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## ABSTRACT

**Background** First-pass effect (FPE), restoring complete or near complete reperfusion (modified Thrombolysis in Cerebral Infarction (mTICI) 2c-3) in a single pass, is an independent predictor for good functional outcomes in the endovascular treatment of acute ischemic stroke. The economic implications of achieving FPE have not been assessed.

**Objective** To assess the economic impact of achieving complete or near complete reperfusion after the first pass.

**Methods** Post hoc analyses were conducted using ARISE II study data. The target population consisted of patients in whom mTICI 2c-3 was achieved, stratified into two groups: (1) mTICI 2c-3 achieved after the first pass (FPE group) or (2) after multiple passes (non-FPE group). Baseline characteristics, clinical outcomes, and healthcare resource use were compared between groups. Costs from peer-reviewed literature were applied to assess cost consequences from the perspectives of the United States (USA), France, Germany, Italy, Spain, Sweden, and United Kingdom (UK).

**Results** Among patients who achieved mTICI 2c-3 (n=172), FPE was achieved in 53% (n=91). A higher proportion of patients in the FPE group reached good functional outcomes (90-day modified Rankin Scale score 0-2) 80.46% vs 61.04%, p<0.01. The patients in the FPE group had a shorter mean length of stay (6.10 vs 9.48 days, p<0.01) and required only a single stent retriever, whereas 35% of patients in the non-FPE group required at least one additional device. Driven by improvement in clinical outcomes, the FPE group had lower procedural/hospitalization-related (24-33% reduction) and annual care (11-27% reduction) costs across all countries.

**Conclusions** FPE resulted in improved clinical outcomes, translating into lower healthcare resource use and lower estimated costs.

## INTRODUCTION

Worldwide, stroke is the leading cause of mortality and disability with a substantial economic impact.<sup>1</sup> The direct and indirect costs of stroke were estimated at US\$33.9 billion in the United States (USA) in 2012-2013.<sup>2</sup> Similarly, in Europe, the annual

economic burden was estimated to be €45 billion in the European Union (EU) alone in 2015.<sup>3</sup> Approximately 87% of all strokes are acute ischemic strokes<sup>4</sup> and 24% to 38% of acute ischemic strokes are caused by large vessel occlusions, which are associated with additional costs.<sup>5</sup> A study from the USA demonstrated that total costs per patient were higher for patients with large vessel occlusions than for those without large vessel occlusions (US\$18 815 vs US\$15 174).<sup>6</sup>

Complete reperfusion of brain tissue is the primary goal in treatment of acute ischemic stroke. Rapid revascularization is vital as reduced time from symptom onset to revascularization is strongly correlated with improved clinical and functional outcomes.<sup>7-8</sup> Complete revascularization with mechanical thrombectomy, a cost-effective treatment for patients with acute stroke, might require multiple passes, which prolongs procedure time and increases the risk of arterial endothelial injury.<sup>9-10</sup> Research suggests that first-pass effect (FPE)—that is, restoring complete or near complete reperfusion (modified Thrombolysis in Cerebral Infarction (mTICI) 2c-3) in a single pass, is an independent predictor of good functional outcome (modified Rankin Scale (mRS) score 0-2).<sup>9</sup> Although the clinical benefits of achieving complete or near complete reperfusion after the first pass have been investigated, the potential economic benefit has not been assessed.

The objective of this analysis was to assess the economic impact of achieving complete or near complete reperfusion after the first pass, FPE, as compared with the need for multiple passes to achieve the same level of reperfusion. Clinical outcomes were derived from patient-level data of the ARISE II (Analysis of Revascularization in Ischemic Stroke with EmboTrap) study, and the analysis was done from the perspective of various healthcare systems (USA, France, Germany, Italy, Spain, Sweden, and United Kingdom (UK)).

## METHODS

### Data source

Post hoc analyses were conducted using patient-level data from the ARISE II study, a prospective

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single-arm international multicenter clinical trial, investigating the efficacy and safety of the EmboTrap device (Cerenovus, Irvine, California, USA) in 227 treated patients. Although the EmboTrap device was used in all procedures as a first-line treatment, the technique used in the ARISE II study was based on investigator's choice (ie, the physicians established an appropriate treatment plan based on the subject's medical condition and available diagnostic screening procedures); specific recommendations were not provided for the use of intermediate catheters (data as to whether the stent retriever was 'engulfed' or 'corked' are not available); and pump suction was not used. Details of the ARISE II study are provided in Zaidat *et al* 2018.<sup>11</sup>

### Target population and comparators

Aligned with the ARISE II publication,<sup>11</sup> FPE was defined as complete or near complete reperfusion (mTICI 2c–3) after the first pass with the EmboTrap device. As such, the target population consisted of patients in whom mTICI 2c–3 was achieved (n=172) in the ARISE II population (patients in whom mTICI 2c–3 was not achieved (n=55) were excluded from the analyses to avoid potential selection bias). The target population was then stratified into two groups: (1) patients in whom mTICI 2c–3 was achieved after the first pass (FPE group) or (2) after multiple

passes (non-FPE group). The two groups were defined based on the core laboratory adjudicated mTICI scores measured after the first pass (ie, total number of passes did not affect categorization).

### Primary analyses

Primary analyses were conducted in two steps. First, baseline characteristics, clinical outcomes, and healthcare resource use were evaluated for each group (ie, FPE and non-FPE) using data from the ARISE II study. Second, cost data from peer-reviewed literature were applied to assess cost consequences using a deterministic approach from two different perspectives, provider and payer.

### Baseline characteristics

Baseline characteristics were compared between the FPE and non-FPE groups to examine the risk of systematic bias and confounders (table 1).

### Clinical outcomes

The following clinical outcomes were assessed: core laboratory adjudicated mTICI score after each pass and at the end of the procedure, 90-day mRS score (categorized into good (mRS

**Table 1** Baseline characteristics for the FPE and non-FPE groups

Variable	FPE (n=91)	Non-FPE (n=81)	P Value*
<b>Demographics</b>			
Age, mean (SD)	68.4 (11.9)	67.7 (14.3)	0.70
Sex, male, n (%)	43 (47.3%)	33 (40.7%)	0.39
<b>Vascular risk factors, n (%)</b>			
Hypertension	66 (72.5%)	57 (70.4%)	0.75
Atrial fibrillation	32 (35.2%)	38 (46.9%)	0.12
Diabetes mellitus	16 (17.6%)	17 (21.0%)	0.57
Dyslipidemia	38 (41.8%)	37 (45.7%)	0.61
Smoking	19 (20.9%)	21 (25.9%)	0.43
Previous MI/CAD	23 (25.3%)	11 (13.6%)	0.06
Previous stroke	16 (17.6%)	13 (16.0%)	0.79
<b>Clinical presentation, median (IQR)</b>			
Baseline NIHSS score	16 (11–19)	16 (13–20)	0.40
Baseline systolic BP, mm Hg†	144 (130–158)	148 (134–158)	0.31
Baseline diastolic BP, mm Hg†	80 (70–91)	81 (72–93)	0.29
<b>Occlusion location, n (%)</b>			
Internal carotid artery	14 (15.4%)	13 (16.0%)	0.90
M1 middle cerebral artery	48 (52.7%)	46 (56.8%)	0.60
M2 middle cerebral artery	22 (24.2%)	20 (24.7%)	0.94
Posterior	7 (7.7%)	2 (2.5%)	0.17
<b>Procedural factors</b>			
Time from onset to puncture (min), median (IQR)	214 (161–263)	220 (153–270)	0.54
General anesthesia, n (%)	33 (36.3%)	25 (30.9%)	0.46
IV tPA use, n (%)	59 (64.8%)	56 (69.1%)	0.55
Balloon guide catheter use, n (%)	71 (78.0%)	60 (74.1%)	0.54
Intermediate catheter use, n (%)	20 (22.0%)	41 (50.6%)	<0.01

\*P values presented for t-test beside means, Wilcoxon rank sum (Mann-Whitney) test beside medians, and chi-square or Fisher's exact tests beside proportions.

†Four patients missing data for systolic and diastolic BP.

BP, blood pressure; CAD, coronary artery disease; FPE, first-pass effect; IQR, interquartile range; IV, intravenous; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation; tPA, tissue plasminogen activator.

score 0–2) and excellent (mRS score 0–1) functional outcomes), 90-day mortality, occurrence of symptomatic intracranial hemorrhage within 24 hours postprocedure based on the Heidelberg Bleeding Classification, embolization into new territory, and discharge status (home, acute care facility, or extended care) assessed at 7 days post-procedure.

### Healthcare resource use

Procedural/hospitalization-related resources, associated with the initial stroke, were compared between the FPE and non-FPE groups (total hospital length of stay (LOS), days in the intensive care unit, standard bed days, and devices used during the procedure).

### Economic outcomes

Cost consequences were compared between the FPE and non-FPE groups from the perspective of healthcare systems in the USA, France, Germany, Italy, Spain, Sweden, and UK with two separate time horizons (procedural/hospitalization-related and annual care in the first year after stroke, details provided below). Clinical and healthcare resource use was obtained from the ARISE II study, and country-specific healthcare resource costs were obtained from peer-reviewed literature and public market research reports, which were validated by clinical experts in interviews. All costs were reported as 2020 currencies and 2020 United States dollars (US\$), and were inflated using country-specific inflation indices if required. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement was used for the reporting of the economic analyses.<sup>12</sup>

The procedural/hospitalization-related economic impact was calculated in the following steps. First, the procedural/hospitalization-related healthcare resource use was obtained for patients in the FPE and non-FPE groups from the ARISE II study. Second, country-specific costs valuing those resources were taken from peer-reviewed literature (LOS costs) and public market research reports (device costs).<sup>13–21</sup> The resources captured in the LOS costs were similar across the literature (online supplemental table I). Third, total costs per patient from a provider perspective in the acute care setting were calculated.

The costs per patient arising during the first year after the stroke from a payer perspective were also calculated in three steps. First, proportions of patients achieving each mRS score (ie, mRS 0 to 6) at 90 days were obtained for each group. Second, country-specific annual care costs, based on 90-day mRS score, were obtained from the literature but were not available for Germany and Spain.<sup>16 22–25</sup> The resources captured in the annual care costs mainly focused on direct healthcare resources (online supplemental table I). Third, total costs per patient arising from a payer perspective were calculated.

### Sensitivity analyses

To test the robustness of the results, univariate sensitivity analyses varying key input parameters were conducted. These included analyses with two alternative definitions of FPE<sup>11 26</sup>: (1) 'FPE (mTICI 3)', defined as achieving mTICI 3 after the first pass and (2) 'FPE (mTICI 2b–3)', defined as achieving mTICI 2b–3 after the first pass. Accordingly, based on the chosen definition of FPE, the target population was also adjusted (eg, patients in whom mTICI 3 was not achieved were excluded from the analyses when the definition of FPE was changed to FPE (mTICI 3)). Two additional parameters were also varied: (1) total LOS was varied within its interquartile range (IQR) since this parameter was not normally distributed and (2) country-specific healthcare

resource costs were increased/decreased by 20% as confidence intervals for these costs were not reported in the literature. A hypothetical cost-efficiency analysis was also conducted using a cohort of 200 cases, where the procedural/hospitalization-related impact of using two devices with variable rates of achieving FPE was compared. In this analysis, it was assumed that one device achieved FPE in an additional 5% of the cases as compared with the other device.

### Statistical analyses

Continuous variables were described using the mean or median and standard deviation (SD) or IQR, while categorical variables were described using the number of observations and proportions. Statistical significance testing was based on a p value of <0.05 for the following tests: t-test and Wilcoxon rank-sum (Mann-Whitney) test for continuous variables and chi-square or Fisher's exact test for categorical variables. All statistical analyses of the ARISE II data were performed using Stata 15 (StataCorp, College Station, Texas, USA).

### RESULTS

In the ARISE II study, complete or near complete reperfusion (ie, mTICI 2c–3) was achieved in 76% of the patients (n=172); among these patients, FPE was observed in 53% (n=91) (online supplemental figure I). Baseline characteristics were mostly balanced between the FPE and non-FPE groups. Notably, intermediate catheter use was lower in the FPE group than in the non-FPE group (22.0% vs 50.6%, p<0.01; table 1).

A significantly higher proportion of patients in the FPE group achieved good (mRS 0–2, 80.46% vs 61.04%, p<0.01) or excellent (mRS 0–1, 63.22% vs 46.75%, p=0.03) functional outcomes as compared with patients in the non-FPE group (table 2 and online supplemental figure II). Although the proportion of patients who died or had symptomatic intracranial hemorrhage were lower in the FPE group, the differences were not statistically significant. The proportion of patients who had an embolization into a new territory was significantly lower in the FPE group (2.20% vs 11.11%, p=0.03; table 2). The proportions of patients discharged to their home or to acute/extended care facilities (skilled nursing home, rehabilitation), respectively, were similar between the FPE and non-FPE groups (43.53% and 44.74% discharged to home and 56.47% and 55.26% discharged to acute/extended care facilities, respectively, p=0.88).

Patients in the FPE group required only a single EmboTrap device, whereas 35% of patients in the non-FPE group required at least one additional device. The patients in the FPE group were also discharged significantly earlier with a shorter mean LOS (6.10 (IQR=3.00–8.00) vs 9.48 (IQR=3.00–11.00) days, p<0.01). Patients in the FPE group had significantly fewer mean number of days spent in a standard bed (3.05 (IQR=0.00–5.00) vs 6.13 (IQR=1.00–8.00), p<0.01), whereas the mean number of days spent in the intensive care unit was similar between the two groups (3.39 (IQR=2.00–4.00) vs 3.58 (IQR=2.00–4.00), p=0.70; table 2).

Subsequent to the improvements in clinical outcomes and lower healthcare resource use during the acute care phase, the economic cost assessment accordingly estimated lower costs for the FPE group. When the acute care costs arising within the hospital (ie, procedural/hospitalization-related costs) were assessed, achieving FPE led to potential per-patient cost savings in every country studied (US\$6575 for the USA, €1560 (US\$1833) for France, €2202 (US\$2587) for Germany, €2901 (US\$3409) for Italy, €4548 (US\$5343) for Spain, Kr 29 468 (US\$3364)

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**Table 2** Clinical and healthcare resource use outcomes for the FPE and non-FPE groups

Outcome	FPE (n=91)	Non-FPE (n=81)	P value*
Clinical outcomes			
90-Day mRS score (categorized into good and excellent functional outcomes)†			
Good outcomes (mRS score 0–2), n (%)	70 (80.46%)	47 (61.04%)	<0.01
Excellent outcomes (mRS score 0–1), n (%)	55 (63.22%)	36 (46.75%)	0.03
90-Day mortality,‡ n (%)	5 (5.68%)	11 (13.75%)	0.08
siCH within 24 hours, n (%)	2 (2.20%)	4 (4.94%)	0.42
ENT, n (%)	2 (2.20%)	9 (11.11%)	0.03
Healthcare resource use outcomes			
LOS			
Total LOS, mean (IQR)§	6.10 (3.00–8.00)	9.48 (3.00–11.00)	<0.01
Standard bed days, mean (IQR)¶	3.05 (0.00–5.00)	6.13 (1.00–8.00)	<0.01
ICU days, mean (IQR)**	3.39 (2.00–4.00)	3.58 (2.00–4.00)	0.70

\*P values presented for the following tests: t-test or Wilcoxon rank-sum (Mann-Whitney) test for continuous variables and chi-square or Fisher's exact test for categorical variables.

†Eight patients missing data for 90-day mRS score.

‡Four patients missing data for 90-day mortality.

§Represents the date of discharge minus date of admission to study hospital; seven patients missing data for LOS.

¶Represents the normal ward days; 10 patients missing data for standard bed days.

\*\*Eight patients missing data for ICU days.

ENT, embolization into new territory; FPE, first-pass effect; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; mRS, modified Rankin Scale; NA, not applicable; siCH, symptomatic intracerebral hemorrhage.

for Sweden, and £1751 (US\$2285) for the UK; [table 3](#), online supplemental figure III). Similarly, achieving FPE led to potential per-patient annual care cost savings in the first year after stroke in every country studied (US\$4116 for the USA, €2131 (US\$2503) for France, €701 (US\$823) for Italy, Kr 13 333 for Sweden (US\$1522), and £2132 (US\$2783) for the UK; [table 4](#), online supplemental figure IV).

When the criteria for FPE were defined to be more limited (ie, mTICI 3 after the first pass), this FPE was observed in 57% (n=67) of the patients who finally achieved mTICI 3 (n=118). The FPE (mTICI 3) group was associated with improved clinical outcomes and reduced healthcare resource use as compared with the non-FPE group, including patients with mTICI 2c reperfusion after first-pass (online supplemental table II). Similar to

the main analyses, limiting the FPE group to FPE (mTICI 3) led to potential per-patient procedural/hospitalization-related and annual care cost savings (online supplemental table III). When the criteria for FPE were broadened (ie, defined as mTICI 2b–3 after the first pass), FPE was seen in 56% (n=117) of the patients who finally achieved at least mTICI 2b. Notably, achieving mTICI 2b–3 after the first pass was also associated with improved clinical outcomes and reduced healthcare resource use and costs (online supplemental tables III and IV). Variations of the total LOS within the IQR and increasing or decreasing the costs by 20% did not alter the direction of the results but did change the magnitude of the estimated cost savings (online supplemental table III).

**Table 3** Average per-patient procedural and hospitalization-related healthcare resource use costs for the FPE and non-FPE groups

	US (2020 US\$)	France (2020 €)	Germany (2020 €)	Italy (2020 €)	Spain (2020 €)	Sweden (2020 Kr)	UK (2020 £)
FPE (n=91)							
LOS*	\$9832	€1381	€3096	€3124	€6542	Kr 68 942	£3019
Devices/methods used	\$7886	€2325	€1415	€3458	€2709	Kr 26 424	£2416
Total	\$17 718	€3706	€4511	€6581	€9252	Kr 95 365	£5435
Non-FPE (n=81)							
LOS*	\$13 616	€2146	€4811	€4854	€10 167	Kr 89 376	£3955
Devices/methods used	\$10 678	€3120	€1902	€4628	€3632	Kr 35 457	£3231
Total	\$24 293	€5266	€6713	€9483	€13 799	Kr 124 833	£7186
Difference (2020 currencies)	–\$6575	–€1560	–€2202	–€2901	–€4548	–Kr 29 468	–£1751
Difference (2020 US\$)†	–\$6575	–\$1833	–\$2587	–\$3409	–\$5343	–\$3364	–\$2285

Numbers may not sum due to rounding.

\*Costs for LOS for US, UK, and Sweden were based on total LOS and proportion of standard bed vs intensive care unit days (standard bed and intensive care unit days costed separately). Costs for LOS for France, Italy, Spain, and Germany were based on total LOS (separate costs for intensive care unit stay and standard bed days not found in the literature; as such, a general cost for LOS was used).

†Exchange rates reported for August 03, 2020, 16:00 UTC were used. The exchange rates were as follows: €1.00=US\$1.17, Kr1.00=US\$0.11, and £1.00=US\$1.31.

FPE, first-pass effect; LOS, length of stay; UTC, coordinated universal time.

**Table 4** Average per-patient annual care costs, based on 90-day mRS score, for the FPE and non-FPE groups

mRS score	% Achieving mRS score		Average costs for annual care/mRS score by country				
	FPE (n=91)	Non-FPE (n=81)	US (2020 US\$)	France (2020 €)	Italy (2020 €)	Sweden (2020 Kr)	UK (2020 £)
0	41.38%	19.48%	\$12 176	€12 817	€2072	Kr 74 717	£3255
1	21.84%	27.27%	\$12 538	€12 817	€2437	Kr 98 093	£3829
2	17.24%	14.29%	\$14 504	€12 817	€2803	Kr 153 609	£4403
3	9.20%	7.79%	\$24 905	€22 244	€5524	Kr 186 481	£15 666
4	2.30%	11.69%	\$50 408	€40 144	€7474	Kr 244 084	£21 196
5	2.30%	5.19%	\$74 108	€40 144	€16 599	Kr 297 096	£34 418
6	5.75%	14.29%	–	–	–	–	–
Results by country							
FPE (n=91)			\$15 430	€14 203	€2934	Kr 108 413	£5661
Non-FPE (n=81)			\$19 546	€16 334	€3635	Kr 121 746	£7794
Difference (2020 currencies)			–\$4116	–€2131	–€701	–Kr 13 333	–£2132
Difference (2020 US\$)*			–\$4116	–\$2503	–\$823	–\$1522	–\$2783

Numbers may not sum due to rounding.

\*Exchange rates reported for August 03, 2020, 16:00 UTC were used. The exchange rates were as follows: €1.00=US\$1.17, Kr1.00=US\$0.11, and £1.00=US\$1.31.

FPE, first-pass effect; mRS, modified Rankin Scale; UTC, coordinated universal time.

In the hypothetical analysis that applied procedural/hospitalization-related costs for the FPE versus non-FPE groups (eg, for the US analyses, per-patient costs for the FPE and non-FPE group were \$17 718 and \$24 293, respectively) and assessed the impact of two devices with variable rates of achieving FPE in a cohort of 200 a per year, the device that achieved a 5% higher FPE rate led to cost savings of US\$65 753 in the USA, US\$18 328 in France, US\$25 868 in Germany, US\$34 087 in Italy, US\$53 433 in Spain, US\$33 637 in Sweden, and US\$22 847 in the UK.

## DISCUSSION

We assessed the economic impact of achieving FPE in patients with acute ischemic stroke from the perspective of healthcare systems in the USA, France, Germany, Italy, Spain, Sweden, and UK using patient-level data from the ARISE II study and cost data from peer-reviewed literature. The results demonstrated that patients achieving FPE had improved functional outcomes, lower risk for embolization into a new territory, and a faster recovery time (shorter LOS). These clinical improvements led to reduced procedural/hospitalization-related and annual care costs in every country studied. The findings proved to be robust after conducting a range of sensitivity analyses that varied key inputs, including the definition of FPE.

The clinical findings in this analysis of the ARISE II data are supported by previous literature.<sup>9,26</sup> Zaidat *et al* demonstrated that patients in the North American Solitaire Stent Retriever Acute Stroke (NASA) registry (n=354) with FPE had improved functional outcomes (90-day good functional outcome: 55.1% vs 31.3%,  $p<0.01$ ) and reduced mortality (16.3% vs 36.5%,  $p<0.01$ ) as compared with patients without FPE.<sup>9</sup> Similarly, a study by Nikoubashman with 164 consecutive patients in whom mTICI 3 was achieved showed that complete reperfusion after the first pass was associated with improved functional outcomes (90-day good functional outcome: 62% vs 40%,  $p=0.013$ ).<sup>26</sup> Additionally, the association between FPE and favorable clinical outcome (mRS score at 90 days of 0–2 or equal to pre-stroke mRS score) has been shown to be independent of the technique used (stent retriever vs aspiration,  $p=0.29$ ).<sup>27</sup>

This analysis demonstrated that achieving mTICI 2c–3 after the first pass was associated with reduced healthcare resource

use. Patients in the FPE group required fewer thrombectomy devices; the number of devices used to achieve mTICI 2c–3 is inevitably linked to the number of passes even though up to three attempts with the same device were allowed in the EmboTrap instructions for use. Patient recovery was faster for patients with FPE as indicated by the significantly shorter total hospital LOS. As such, achieving mTICI 2c–3 after the first pass led to potential per-patient procedural/hospitalization-related cost savings in every country studied. Notably, the reductions in healthcare resource use and cost savings were driven by the improvements in clinical outcomes. An analysis of the GAIN international trial demonstrated that LOS in hospital during the first 90 days after a stroke was positively associated with 90-day mRS score.<sup>28</sup> Long-term direct healthcare costs of stroke are mainly driven by patients who do not achieve functional recovery and their degree of disability.<sup>29,30</sup> Thus, due to the higher rate of patients achieving functional independence in the FPE group, our analysis showed that patients in the FPE group had lower costs in the first year after stroke than those in the non-FPE group. These findings are also aligned with a recent Markov model that showed that achieving expanded TICI (eTICI) 3 resulted in healthcare (US\$10 327) and societal (US\$20 224) cost savings as compared with achieving eTICI 2b among patients with large vessel occlusions.<sup>31</sup>

Rapid revascularization is widely accepted to be strongly correlated with improved clinical outcomes.<sup>7,8</sup> It might be argued that the improvements in clinical outcomes seen in this study were not due to FPE per se but due to the prolonged time between groin puncture and reperfusion associated with multiple passes.<sup>26</sup> However, a matched case–control analysis that adjusted for time from symptom onset to complete reperfusion showed that the occurrence of good functional outcomes was almost twice as common among those who achieved complete reperfusion after the first pass as compared with those who achieved complete reperfusion after multiple passes.<sup>26</sup> Additionally, Garcia-Tornel and colleagues reported a linear association between the number of passes and good functional outcomes among patients who underwent mechanical thrombectomy procedures for large vessel occlusion in the anterior circulation and achieved recanalization as compared with patients who did not achieve recanalization.<sup>32</sup> Jindal *et al* also reported that the

proportion of patients who achieved good functional outcome was inversely related to the number of passes among anterior cerebral circulation stroke thrombectomy cases.<sup>33</sup> Similarly, multivariable analyses from Zaidat *et al* demonstrated that achieving FPE was an independent predictor of good functional outcome.<sup>9</sup>

Although there are factors that might affect the likelihood of achieving FPE (eg, factors related to the treating physician such as training, settings such as available equipment, and patients such as clot composition), recent research has suggested that certain techniques involving the combined use of stent retrievers and intermediate aspiration catheters could improve recanalization rates and the rate of FPE.<sup>34 35</sup> Thus it might be beneficial to 'throw everything in' immediately to improve the likelihood of achieving FPE. In this context it might be surprising that the use of intermediate catheters was less frequent in the FPE group than in the non-FPE group (22.0% vs 50.6%,  $p < 0.01$ ), as several published techniques (eg, SAVE, PROTECT<sup>PLUS</sup>) that incorporate intermediate catheters report a high percentage of FPE.<sup>34 36</sup> Potential explanations for the higher use of intermediate catheters in the non-FPE versus FPE group include electing to use the intermediate catheter after first-pass failure (perhaps, due to thrombus composition and/or lack of standardized practices).

Research examining the reasons for improved clinical outcomes with FPE is ongoing; current literature suggests that repeated thrombectomy passes may be associated with an increased risk of vessel injury and distal embolization, which could negatively impact clinical outcomes.<sup>9 26</sup> Additionally, more passes increase the risk of losing embolic fragments into previously unaffected territories. This hypothesis is supported by the results of this study, which showed that the proportion of patients who had embolization into a new territory was significantly lower in the FPE group than in the non-FPE group (2.20% vs 11.11%,  $p = 0.03$ ). Both distal embolization and embolization into new vascular territories damage brain tissue directly and can also cut off leptomeningeal collaterals and thus accelerate dying of penumbral tissue.

This study has several strengths, including the use of patient-level data from a multi-country study to inform the health economic analyses, inclusion of several countries in the health economic analyses for increased generalizability, and differentiation between acute and annual care costs. Furthermore, as compared with previous literature,<sup>9</sup> the target population for this study excluded patients for whom mTICI 2c–3 was not achieved to obtain a homogeneous patient cohort and to conduct an unbiased assessment of FPE. However, the findings of this study should be interpreted in the context of the following limitations. First, there were limitations in relation to the procedural/hospitalization-related and annual care cost data used in this analysis, which were obtained from the literature. There were differences in resources captured in costs across countries and in the patient populations that were assessed in the cost literature and in the ARISE II study, respectively.<sup>16 23 25</sup> However, this study used the best available cost estimates, which were validated by clinical experts in interviews. Second, it is plausible that resource use may vary across countries owing to variations in clinical practices. Sensitivity analyses assessing differences by region were not feasible due to small sample sizes. Third, procedural/hospitalization-related and annual care costs were not comprehensive. Analyses assessing the procedural/hospitalization-related economic impact did not include costs for procedure time and intermediate catheters (lower use in the FPE group), and analyses assessing the annual care economic impact did not include costs for death (ie, mRS score 6), which

had a lower incidence in the FPE group. Fourthly, the economic impact of FPE was assessed in a deterministic analysis (ie, a probabilistic model was not created as we used point estimates from one clinical study and costs from the literature, which often did not report the associated measures of variability). However, we used the best available estimates for all key inputs and conducted numerous sensitivity analyses, including those that altered the definition of FPE.

## CONCLUSIONS

According to our knowledge, this is the first study which assesses the health economic impact of FPE. The analysis showed that patients in the FPE group had improved clinical outcomes as compared with patients in the non-FPE group, which resulted in lower healthcare resource use and improved economic outcomes. Overall, the findings indicate that the performance within the thrombectomy procedure affects both the clinical outcome and healthcare spending in the short and long term. Thus FPE represents a relevant procedural goal for endovascular treatment of acute ischemic stroke. Moreover, the first-line treatment should ideally involve a thrombectomy technique that provides the best chance of succeeding in the first pass. Future economic studies that obtain clinical and economic data from the same data source are required to validate the findings from these analyses. Additionally, studies are required to determine the factors and techniques/methods that maximize the likelihood of achieving FPE.

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**Competing interests** Ooz serves as a consultant for Neuravi, Stryker, Penumbra, and Medtronic. MR is a shareholder in Anaconda Biomed; consultant for Neuravi/Cerenovus, Medtronic, Stryker, Apta Targets, and Vesalio. HPM reports personal fees from Covidien/Medtronic, Neuravi/Cerenovus, Servier, and Bayer outside the submitted work; served on the steering committees of the SWIFT PRIME and ARISE studies. JLS is an employee of the University of California, which holds a patent on retriever devices for stroke. The University of California, Regents receives funding for the services of JLS as a scientific consultant regarding trial design and conduct to Covidien/Medtronic and Stryker; serves as a consultant for Modest, Abbott, Medtronic, Stryker, and Neuravi/Cerenovus; has contracted stock options for Modest and Rapid Medical. HB serves as a modest consultant for Neuravi/Cerenovus, and Stryker. AJY is a consultant for Cerenovus, Penumbra, Genentech, and Zoll Circulation; receives research grant support from Cerenovus, Penumbra, Medtronic, Stryker, and Genentech; and has equity interest in Insera Therapeutics. AE is an employee of Johnson and Johnson. EK is an employee of Cerenovus, a subsidiary of Johnson and Johnson. HLC and RAQ are paid consultants for Cerenovus. TA is a consultant for Neuravi/Cerenovus, Anaconda, Amnis Therapeutics, and Rapid Medical; served on the steering committees of the ARISE studies.

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SUPPLEMENTAL MATERIALS

## 1.0 Supplemental Tables

**Supplemental Table I. Sources used to obtain costs for analyses**

Study/Source	Country	Currency	Components included in costs	Cost (reported year currency)	Cost (2020 currency)
LOS cost per day					
Gershengorn (2015)[1]	US	2013 USD	Daily costs for quaternary surgical ICU	\$1766.67	\$2,138.79
Chen (2019)[2]		2018 USD	Average cost for ward cost per day across bariatric, colectomy, hepatic resection, lobectomy, and hysterectomy procedures in Americas	\$966.22	\$1,025.97
ENC MCO (2016)	France	2016 Euros	Medical professionals, pharmacy, and overhead (e.g. cleaning, laundry)	€226.28	€226.39
Dodel (2004)[3]	Germany	2002 Euros	Diagnostic procedures, medical treatment, drugs, physiotherapy, speech therapy, nursing, and nonmedical supplies	€360.00	€507.48
Fattore (2012)[4]	Italy	2007 Euros	Resources used during the index hospitalization (e.g. drugs, imaging and laboratory exams, consumables, medical procedures, consultation visits, inpatient rehabilitation)	€412.81	€512.07
Vega-Valdes (2018)[5]	Spain	2016 Euros	Diagnostic procedures and medical treatment	€1,051.54	€1,072.48
Carlsson (2017)[6]	Sweden	2015 Swedish Krona	Resources used in a neurological ICU and the neurological department	ICU: SEK 16,223.42 SBD: SEK 4,836.08	ICU: SEK 16,929.79 SBD: SEK 5,046.64
Ming Xu (2018)[7]	UK	2015 Pounds	Resources used in an acute stroke unit and a general medical ward	ICU: £649.00 SBD: £210.00	ICU: £728.18 SBD: £235.62
Device cost					
Internal market research for	US	-	Stent retrievers and aspiration devices	-	Stent retriever: \$7,852 Aspiration device: \$5,415

Study/Source	Country	Currency	Components included in costs	Cost (reported year currency)	Cost (2020 currency)
stent retrievers and Vidal (2016)[8] for aspiration devices					
Internal market report[9]	France	-		-	Stent retriever: €2,300.00 Aspiration device: €932.00
	Germany	-		-	Stent retriever: €1,400.00 Aspiration device: €673.00
	Italy	-		-	Stent retriever: €3,420.00 Aspiration device: €946.00
	Spain	-		-	Stent retriever: €2,680.00 Aspiration device: €963.00
	Sweden	-		-	Stent retriever: SEK 26,136.04 Aspiration device: SEK 10,685.30
	UK	-		-	Stent retriever: £2,390.00 Aspiration device: £517.00
Cost per mRS score(s)					
Shireman (2017)[10]	US	2015 USD	Inpatient and outpatient costs including nursing home costs using data from the National Death Index and Centers for Medicare and Medicaid Services (CMS)	mRS 0: \$10,569.00 mRS 1: \$10,883.00 mRS 2: \$12,590.00 mRS 3: \$21,618.00 mRS 4: \$43,755.00 mRS 5: \$64,327.00	mRS 0: \$12,176.06 mRS 1: \$12,537.81 mRS 2: \$14,504.36 mRS 3: \$24,905.11 mRS 4: \$50,408.13 mRS 5: \$74,108.19
Spieler (2004)[11]	France	1997 Euros	Ambulatory care, orthosis, drugs, convalescent home, rehabilitation, new acute hospitalization, nursing home, and long-term chronic hospitalization	mRS 0-2: €10,000.00 mRS 3: €17,355.37 mRS 4-5: €31,322.31	mRS 0-2: €12,816.51 mRS 3: €22,243.53 mRS 4-5: €40,144.27
Fattore (2012)[4]	Italy	2007 Euros	Resources used from discharge to 12 months (e.g. hospital admissions, clinical consultations, diagnostic procedures, domiciliary care,	mRS 0-2: €1,964.80* mRS 3: €5,239.10* mRS 4-5: €13,381.50*	mRS 0: €2,071.65 mRS 1: €2,437.23 mRS 2: €2,802.82 mRS 3: €5,524.01

Study/ Source	Country	Currency	Components included in costs	Cost (reported year currency)	Cost (2020 currency)
			medical therapies, rehabilitation services, number of general practitioner visits, days of work lost, number of hours of informal care)		mRS 4: €7,473.66 mRS 5: €16,599.06
Dental and Pharmaceutical Benefits Agency (TLV)[12]	Sweden		Resources used for annual post acute care (healthcare professional time, emergency care, outpatient visits, day cases and hospitalisations)	mRS 0: SEK 71,600.00 mRS 1: SEK 94,000.00 mRS 2: SEK 147,200.00 mRS 3: SEK 178,700.00 mRS 4: SEK 233,900.00 mRS 5: SEK 284,700.00	mRS 0: SEK 74,717.49 mRS 1: SEK 98,092.80 mRS 2: SEK 153,609.15 mRS 3: SEK 186,480.67 mRS 4: SEK 244,084.10 mRS 5: SEK 297,095.95
Lobotesis (2016)[13]	UK	2014 Pounds	Long-term accommodation in warden housing and nursing or residential care	mRS 0: £2,846.00 mRS 1: £3,348.00 mRS 2: £3,850.00 mRS 3: £13,697.00 mRS 4: £18,532.00 mRS 5: £30,093.00	mRS 0: £3,255.06 mRS 1: £3,829.21 mRS 2: £4,403.36 mRS 3: £15,665.68 mRS 4: £21,195.62 mRS 5: £34,418.29

\* Although Fattore (2012) reported costs for aggregate mRS scores (i.e. mRS 0-2, mRS 3, mRS 4-5), they were converted to costs per individual mRS score (i.e. mRS 0 to 6) based on an Italian cost-effectiveness analysis.<sup>14</sup>

Abbreviations: ENC = L'Etude nationale des coûts; ICU = intensive care unit; LOS = length of stay; MCO = médecine, chirurgie, obstétrique et odontologie; mRS = modified Rankin Scale; NR = not reported; SBD = standard bed day; SEK = Swedish Krona; UK = United Kingdom; US = United States; USD = United States Dollars.

**Supplemental Table II. Clinical and healthcare resource use outcomes for the FPE (mTICI 3) and non-FPE (mTICI 3) groups**

Outcome	FPE (mTICI 3) (n=67)	Non-FPE (mTICI 3) (n=51)	P-Value*
<b>Clinical outcomes</b>			
90-day mRS (categorized into good and excellent functional outcomes) <sup>†</sup>			
90-day mRS, good outcomes (mRS 0-2), n (%)	50 (78.13%)	30 (62.50%)	0.07
90-day mRS, excellent outcomes (mRS 0-1), n (%)	40 (62.50%)	26 (54.17%)	0.38
90-day mortality <sup>‡</sup>			
90-day mortality, n (%)	5 (7.69%)	7 (13.73%)	0.29
sICH within 24-hours			
sICH within 24-hours, n (%)	2 (2.99%)	1 (1.96%)	1.00
ENT			
ENT, n (%)	1 (1.49%)	6 (11.76%)	0.04
<b>Healthcare resource use outcomes</b>			
<b>LOS</b>			
Total LOS, mean (IQR) <sup>§</sup>	6.22 (3.00 – 8.00)	9.56 (3.00 – 11.75)	0.03
Standard bed days, mean (IQR) <sup>  </sup>	3.08 (0.00 – 5.00)	6.46 (1.00 – 9.25)	0.03
ICU days, mean (IQR) <sup>#</sup>	3.56 (2.00 – 4.00)	3.38 (2.00 – 4.00)	0.77
<b>Additional devices used during procedure</b>			
Stent retrievers, %	0%	37.25%	NA
Aspiration devices, %	0%	1.96%	NA

\* P-values presented for the following tests: t-test and Wilcoxon rank-sum (Mann-Whitney) test for continuous variables and chi-square or Fisher's exact test for categorical variables.

<sup>†</sup> Six patients missing data for 90-day mRS.

<sup>‡</sup> Two patients missing data for 90-day mortality.

<sup>§</sup> Represents the date of discharge minus date of admission to study hospital; five patients missing data for LOS.

<sup>||</sup> Represents the normal ward days; seven patients missing data for standard bed days.

<sup>#</sup> Five patients missing data for ICU days.

Abbreviations: ENT = embolization into new territory; FPE = first pass effect; ICU = intensive care unit; IQR = interquartile range; LOS = length of stay; mRS = modified Rankin Scale; NA = not applicable; sICH = symptomatic intracerebral hemorrhage.

**Supplemental Table III. Cost differences from sensitivity analyses comparing average per-patient procedural and hospitalization-related and annual care costs for the FPE and non-FPE groups**

	US	France		Germany		Italy		Spain		Sweden		UK	
Currency (2020)	USD	€	USD*	€	USD*	€	USD*	€	USD*	SEK	USD*	£	USD*
Base-case (cost differences)													
Procedural and hospitalization-related	-6,575	-1,560	-1,833	-2,202	-2,587	-2,901	-3,409	-4,548	-5,343	-29,468	-3,364	-1,751	-2,285
Annual care	-4,116	-2,131	-2,503	NA <sup>†</sup>	NA <sup>†</sup>	-701	-823	NA <sup>†</sup>	NA <sup>†</sup>	-13,333	-1,522	-2,132	-2,783
Sensitivity analyses (cost differences)													
Alternative definitions of FPE													
FPE (mTICI 3)													
Procedural and hospitalization-related	-6,429	-1,631	-1,916	-2,230	-2,620	-3,003	-3,528	-4,599	-5,404	-26,195	-2,990	-1,662	-2,169
Annual care	-4,338	-2,115	-2,485	NA <sup>†</sup>	NA <sup>†</sup>	-809	-950	NA <sup>†</sup>	NA <sup>†</sup>	-10,683	-1,219	-2,133	-2,783
FPE (mTICI 2b-3)													
Procedural and hospitalization-related	-4,689	-1,261	-1,482	-1,871	-2,198	-2,393	-2,811	-3,878	-4,556	-17,206	-1,964	-1,119	-1,461
Annual care	-6,010	-3,141	-3,690	NA <sup>†</sup>	NA <sup>†</sup>	-1,087	-1,278	NA <sup>†</sup>	NA <sup>†</sup>	-18,941	-2,162	-3,142	-4,101
Variations in LOS around the first and third quartile <sup>‡</sup>													
LOS (first quartile)													
Procedural and hospitalization-related	-2,265	-795	-934	-486	-572	-1,170	-1,375	-923	-1,084	-3,411	-389	-581	-759
LOS (third quartile)													
Procedural and hospitalization-related	-5,696	-1,474	-1,732	-2,009	-2,360	-2,707	-3,180	-4,140	-4,864	-22,323	-2,548	-1,445	-1,885
Variations in costs													
Increased by 20%													
Procedural and hospitalization-related	-7,890	-1,872	-2,199	-2,642	-3,104	-3,482	-4,090	-5,457	-6,412	-35,362	-4,036	-2,101	-2,742
Annual care	-4,939	-2,557	-3,004	NA <sup>†</sup>	NA <sup>†</sup>	-841	-988	NA <sup>†</sup>	NA <sup>†</sup>	-15,999	-1,826	-2,559	-3,339
Decreased by 20%													

	US	France		Germany		Italy		Spain		Sweden		UK	
Currency (2020)	USD	€	USD*	€	USD*	€	USD*	€	USD*	SEK	USD*	£	USD*
Procedural and hospitalization-related	-5,260	-1,248	-1,466	-1,761	-2,069	-2,321	-2,727	-3,638	-4,275	-23,575	-2,691	-1,401	-1,828
Annual care	-3,293	-1,705	-2,003	NA <sup>†</sup>	NA <sup>†</sup>	-561	-659	NA <sup>†</sup>	NA <sup>†</sup>	-10,666	-1,218	-1,706	-2,226

Negative values indicate cost savings for the FPE group as compared with the non-FPE group.

\* Exchange rates reported for August 03, 2020, 16:00 UTC were used. The exchange rates were as follows: 1.00 EUR: 1.17 USD, 1.00 SEK: 0.11 USD and 1.00 GBP: 1.31 USD.

<sup>†</sup> Annual care costs, based on 90-day mRS, were not found for Germany and Spain.

<sup>‡</sup> LOS was varied within its IQR since this parameter was not normally distributed. Additionally, variations in LOS did not impact annual care costs.

Abbreviations: FPE = first pass effect; GBP = Great British Pound; IQR = interquartile range; LOS = length of stay; mTICI = modified Thrombolysis in Cerebral Infarction; NA = not applicable; SEK = Swedish Krona; UK = United Kingdom; US = United States; USD = United States Dollar; UTC = Coordinated Universal Time.

**Supplemental Table IV. Clinical outcomes for the FPE (mTICI 2b-3) and non-FPE (mTICI 2b-3) groups**

Outcome	FPE (mTICI 2b-3) (n=117)	Non-FPE (mTICI 2b-3) (n=93)	P-Value*
<b>Clinical outcomes</b>			
<b>90-day mRS (categorized into good and excellent functional outcomes)<sup>†</sup></b>			
90-day mRS, good outcomes (mRS 0-2), n (%)	89 (79.46%)	48 (54.55%)	<0.01
90-day mRS, excellent outcomes (mRS 0-1), n (%)	70 (62.50%)	37 (42.05%)	<0.01
<b>90-day mortality<sup>‡</sup></b>			
90-day mortality, n (%)	5 (4.42%)	12 (13.04%)	0.03
<b>sICH within 24-hours</b>			
sICH within 24-hours, n (%)	2 (1.71%)	7 (7.53%)	0.08
<b>ENT</b>			
ENT, n (%)	4 (3.42%)	10 (10.75%)	0.03
<b>Healthcare resource use outcomes</b>			
<b>LOS</b>			
Total LOS, mean (IQR) <sup>§</sup>	6.38 (3.00 – 8.00)	9.36 (3.00 – 11.00)	<0.01
Standard bed days, mean (IQR) <sup>  </sup>	3.16 (0.00 – 5.00)	7.22 (1.00 – 9.00)	<0.01
ICU days, mean (IQR) <sup>#</sup>	3.51 (2.00 – 4.00)	3.37 (1.50 – 4.00)	0.77
<b>Additional devices used during procedure</b>			
Stent retrievers, %	5.13%	30.11%	NA
Aspiration devices, %	0.85%	2.16%	NA

\* P-values presented for the following tests: t-test and Wilcoxon rank-sum (Mann-Whitney) test for continuous variables and chi-square or Fisher's exact test for categorical variables.

<sup>†</sup> Ten patients missing data for 90-day mRS.

<sup>‡</sup> Five patients missing data for 90-day mortality.

<sup>§</sup> Represents the date of discharge minus date of admission to study hospital; nine patients missing data for LOS.

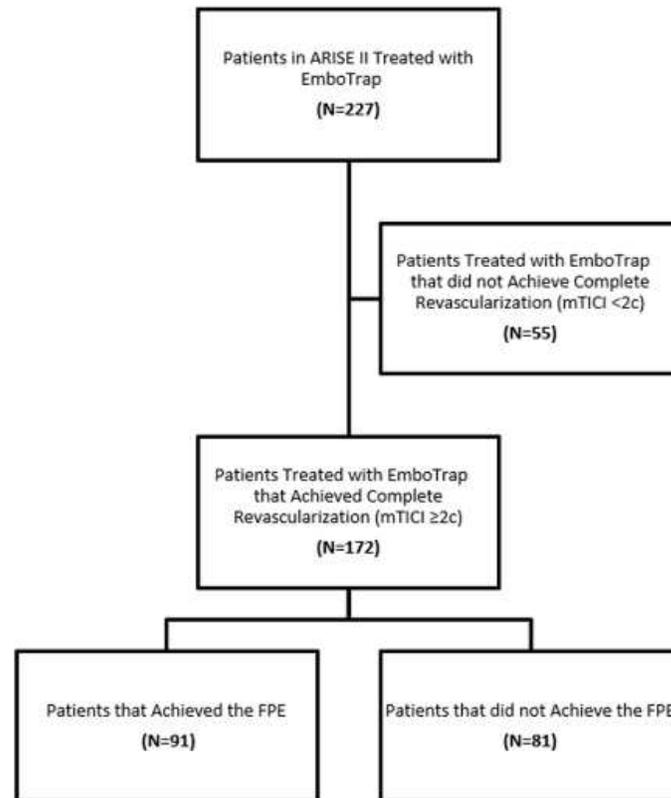
<sup>||</sup> Represents the normal ward days; ten patients missing data for standard bed days.

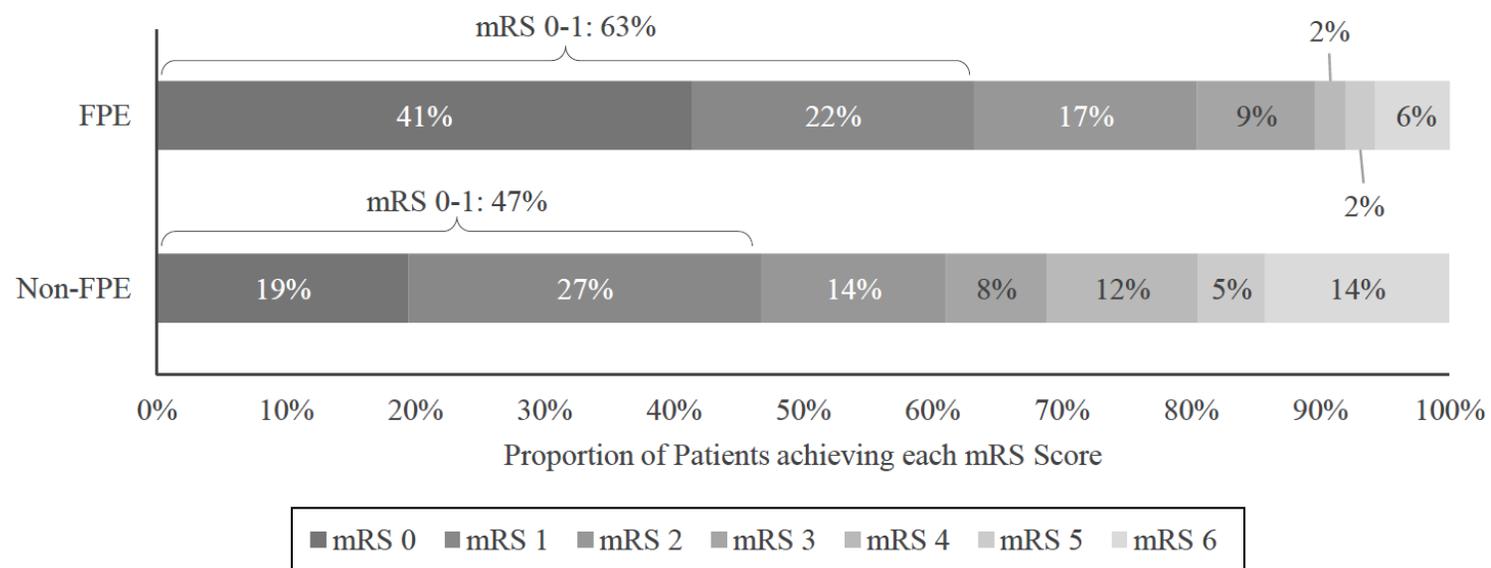
<sup>#</sup> Eight patients missing data for ICU days.

Abbreviations: ENT = embolization into new territory; FPE = first pass effect; ICU = intensive care unit; IQR = interquartile range; LOS = length of stay; mRS = modified Rankin Scale; NA = not applicable; sICH = symptomatic intracerebral hemorrhage.

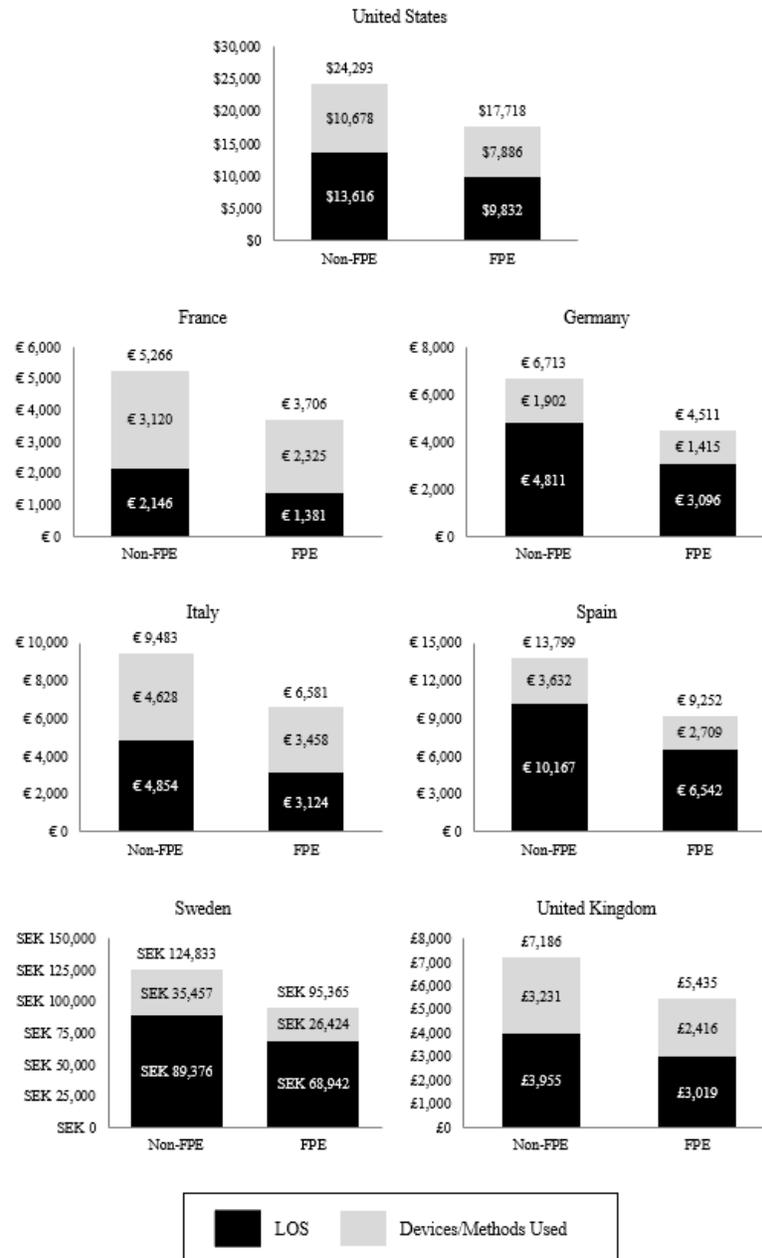
## 2.0 Supplemental Figures

### Supplemental Figure I. Patient flowchart displaying the number of patients who did or did not achieve FPE in ARISE II

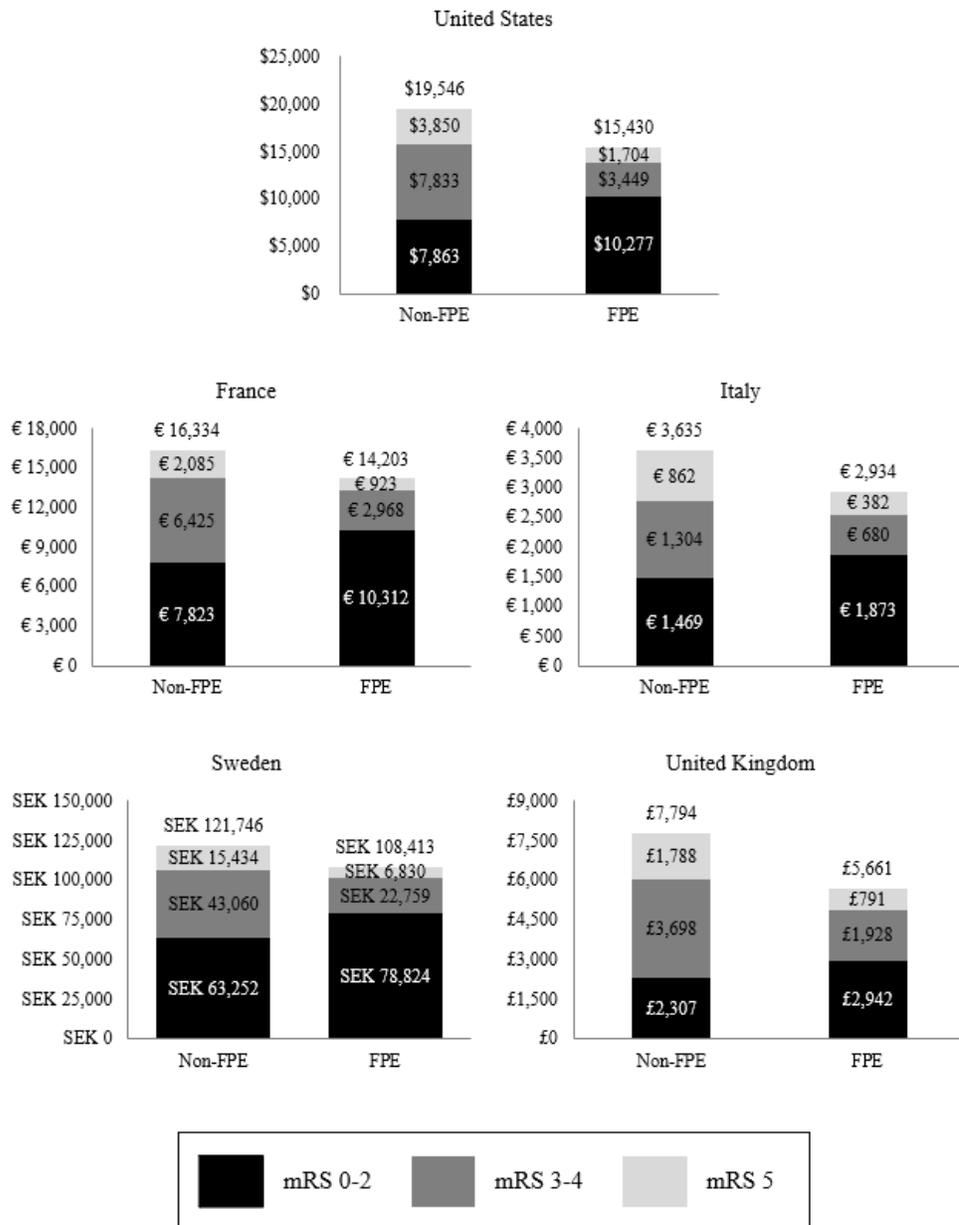


**Supplemental Figure II. Proportion of patients achieving each mRS score among the FPE and non-FPE groups**

**Supplemental Figure III. Average per-patient procedural and hospitalization-related healthcare resource use costs for the FPE and non-FPE groups**



**Supplemental Figure IV. Average per-patient annual care costs, based on 90-day mRS, for the FPE and non-FPE groups**



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