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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.[1] The direct and indirect costs of stroke were estimated at US$33.9 billion in the United States (USA) in 2012–2013.[2] Similarly, in Europe, the annual economic burden was estimated to be €45 billion in the European Union (EU) alone in 2015.[3] Approximately 87% of all strokes are acute ischemic strokes[4] and 24% to 38% of acute ischemic strokes are caused by large vessel occlusions, which are associated with additional costs.[5] 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).[6]

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.[7 8] 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.[9 10] 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).[9] 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

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.[11]

Target population and comparators

Aligned with the ARISE II publication,[11] 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*
Demographics			
Age, mean (SD)	68.4 (11.9)	67.7 (14.3)	0.70
Sex, male, n (%)	43 (47.3%)	33 (40.7%)	0.39
Vascular risk factors, n (%)			
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
Clinical presentation, median (IQR)			
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
Occlusion location, n (%)			
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
Procedural factors			
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.[12]

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).[13–21] 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.[16 22–25] 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[11 26]: (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)

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

	% Achieving mRS score		Average costs for annual care/mRS score by country				
mRS score	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.[9 26] 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.[9] 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).[26] 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).[27]

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.[28] Long-term direct healthcare costs of stroke are mainly driven by patients who do not achieve functional recovery and their degree of disability.[29 30] 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.[31]

Rapid revascularization is widely accepted to be strongly correlated with improved clinical outcomes.[7 8] 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.[26] 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.[26] 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.[32] 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.[33] Similarly, multivariable analyses from Zaidat *et al* demonstrated that achieving FPE was an independent predictor of good functional outcome.[9]

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.[34 35] 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^{PLUS}) that incorporate intermediate catheters report a high percentage of FPE.[34 36] 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.[9 26] 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,[9] 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.[16 23 25] 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.

Patient consent for publication Not required.

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REFERENCES

1 GBD 2016 Stroke Collaborators. Global, regional, and national burden of stroke, 1990-2016: a systematic analysis for the global burden of disease study 2016. *Lancet Neurol* 2019;18:439–58.
2 Benjamin EJ, Blaha MJ, Chiuve SE, *et al*. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. *Circulation* 2017;135:e146–603.
3 Wilkins E, Wilson L, Wickramasinghe K, *et al*. *European cardiovascular disease statistics 2017*, 2017.
4 Centers for Disease Control and Prevention (CDC). *Stroke facts*, 2020.
5 Rennert RC, Wali AR, Steinberg JA, *et al*. Epidemiology, natural history, and clinical presentation of large vessel ischemic stroke. *Neurosurgery* 2019;85:S4–8.
6 Rai AT, Evans K, Riggs JE, *et al*. Intravenous thrombolysis of large vessel occlusions is associated with higher hospital costs than small vessel strokes: a rationale for developing stroke severity-based financial models. *J Neurointerv Surg* 2016;8:423–8.
7 Goyal M, Jadhav AP, Bonafe A, *et al*. Analysis of workflow and time to treatment and the effects on outcome in endovascular treatment of acute ischemic stroke: results from the SWIFT PRIME randomized controlled trial. *Radiology* 2016;279:888–97.
8 Shi Z-S, Liebeskind DS, Xiang B, *et al*. Predictors of functional dependence despite successful revascularization in large-vessel occlusion strokes. *Stroke* 2014;45:1977–84.
9 Zaidat OO, Castonguay AC, Linfante I, *et al*. First pass effect: a new measure for stroke thrombectomy devices. *Stroke* 2018;49:660–6.
10 Khunte M, Wu X, Payabvash S, *et al*. Cost-effectiveness of endovascular thrombectomy in patients with acute stroke and M2 occlusion. *J Neurointerv Surg* 2020. doi:10.1136/neurintsurg-2020-016765. [Epub ahead of print: 19 Oct 2020].
11 Zaidat OO, Bozorgchami H, Ribó M, *et al*. Primary results of the multicenter ARISE II study (Analysis of Revascularization in Ischemic Stroke with EmboTrap). *Stroke* 2018;49:1107–15.
12 Husereau D, Drummond M, Petrou S, *et al*. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *Cost Eff Resour Alloc* 2013;11:6.
13 Gershengorn HB, Garland A, Gong MN. Patterns of daily costs differ for medical and surgical intensive care unit patients. *Ann Am Thorac Soc* 2015;12:1831–6.
14 Chen BP, Clymer JW, Turner AP, *et al*. Global hospital and operative costs associated with various ventral cavity procedures: a comprehensive literature review and analysis across regions. *J Med Econ* 2019;22:1210–20.
15 Dodel RC, Haacke C, Zamzow K, *et al*. Resource utilization and costs of stroke unit care in Germany. *Value Health* 2004;7:144–52.
16 Fattore G, Torbica A, Susi A, *et al*. The social and economic burden of stroke survivors in Italy: a prospective, incidence-based, multi-centre cost of illness study. *BMC Neurol* 2012;12:137.
17 Vega Valdés P, Murias Quintana E, Morales Santos E, *et al*. Análisis de los costes directos asociados a la trombectomía mecánica ya la fibrinólisis intravenosa en el Hospital Universitario central de asturias. *Revista de Neurología* 2018;66:7–14.
18 Steen Carlsson K, Andsberg G, Petersson J, *et al*. Long-term cost-effectiveness of thrombectomy for acute ischaemic stroke in real life: an analysis based on data from the Swedish stroke register (Riksstroke). *Int J Stroke* 2017;12:802–14.
19 Xu X-M, Vestesson E, Paley L, *et al*. The economic burden of stroke care in England, Wales and Northern Ireland: using a national stroke register to estimate and report patient-level health economic outcomes in stroke. *Eur Stroke J* 2018;3:82–91.
20 Decision Resource Group (DRG). *Clot management devices: market insights*, 2018.
21 Vidal GA, Milburn JM. The penumbra 5MAX ACE catheter is safe, efficient, and cost saving as a primary mechanical thrombectomy device for large vessel occlusions in acute ischemic stroke. *Ochsner J* 2016;16:486–91.
22 Shireman TI, Wang K, Saver JL, *et al*. Cost-effectiveness of Solitaire stent retriever thrombectomy for acute ischemic stroke: results from the SWIFT-PRIME trial (solitaire with the intention for thrombectomy as primary endovascular treatment for acute ischemic stroke). *Stroke* 2017;48:379–87.
23 Spieler J-F, Lanoë J-L, Amarenco P. Costs of stroke care according to handicap levels and stroke subtypes. *Cerebrovasc Dis* 2004;17:134–42.
24 Dental and Pharmaceutical Benefits Agency (TLV). Cost-effectiveness analysis of thrombectomy for treatment of acute severe ischemic stroke; 2015.
25 Lobotesis K, Veltkamp R, Carpenter IH, *et al*. Cost-effectiveness of stent-retriever thrombectomy in combination with IV t-PA compared with IV t-PA alone for acute ischemic stroke in the UK. *J Med Econ* 2016;19:785–94.
26 Nikoubashman O, Dekeyzer S, Riabikin A, *et al*. True first-pass effect. *Stroke* 2019;50:2140–6.
27 Ducroux C, Piotin M, Gory B, *et al*. First pass effect with contact aspiration and stent retrievers in the aspiration versus stent retriever (ASTER) trial. *J Neurointerv Surg* 2020;12:386–91.
28 Dawson J, Lees JS, Chang T-P, *et al*. Association between disability measures and healthcare costs after initial treatment for acute stroke. *Stroke* 2007;38:1893–8.
29 Kavanagh S, Knapp M, Patel A. Costs and disability among stroke patients. *J Public Health Med* 1999;21:385–94.
30 Luengo-Fernandez R, Yiin GSC, Gray AM, *et al*. Population-based study of acute- and long-term care costs after stroke in patients with AF. *Int J Stroke* 2013;8:308–14.
31 Kunz WG, Almekhlafi MA, Menon BK, *et al*. Public health and cost benefits of successful reperfusion after thrombectomy for stroke. *Stroke* 2020;51:899–907.
32 García-Tornel Álvaro, Requena M, Rubiera M, *et al*. When to stop. *Stroke* 2019;50:1781–8.
33 Jindal G, Carvalho HDP, Wessell A, *et al*. Beyond the first pass: revascularization remains critical in stroke thrombectomy. *J Neurointerv Surg* 2019;11:1095–9.
34 Maegerlein C, Berndt MT, Mönch S, *et al*. Further development of combined techniques using stent retrievers, aspiration catheters and BGC : The PROTECT^{PLUS} Technique. *Clin Neuroradiol* 2020;30:59–65.
35 Delgado Almandoz JE, Kayan Y, Young ML, *et al*. Comparison of clinical outcomes in patients with acute ischemic strokes treated with mechanical thrombectomy using either Solumbra or ADAPT techniques. *J Neurointerv Surg* 2016;8:1123–8.
36 Maus V, Behme D, Kabbasch C, *et al*. Maximizing first-pass complete reperfusion with save. *Clin Neuroradiol* 2018;28:327–38.