Research Article

For reprint orders, please contact: reprints@futuremedicine.com

Journal of **Comparative Effectiveness Research**

Endovascular treatment with the Enterprise stent versus the Neuroform or Low-Profile Visualized Intraluminal Support stent for unruptured aneurysms

Reade De Leacy[1], Emilie Kottenmeier[2], Stephanie HY Lee[3], Rahul Khanna*[,4] & Alejandro M Spiotta[5]

[1]Department of Neurosurgery, Mount Sinai Hospital, New York, NY, USA
[2]Johnson & Johnson Medical Devices, Franchise Health Economics & Market Access, Irvine, CA, USA
[3]Johnson & Johnson Medical Devices, Asia Pacific, Singapore
[4]Medical Device Epidemiology, Johnson & Johnson, New Brunswick, NJ, USA
[5]Department of Neurosurgery, Medical University of South Carolina, Charleston, SC, USA
*Author for correspondence: Tel.: +1 732 524 6075; rkhann14@its.jnj.com

Aim: To compare outcomes among patients undergoing endovascular treatment for unruptured intracranial aneurysm (UIA) with the Enterprise stent versus the Neuroform or Low-Profile Visualized Intraluminal Support (LVIS) stent. **Patients & methods:** Patients undergoing endovascular procedure for UIA were classified into Enterprise stent and Neuroform or LVIS stent group. Groups were propensity-score matched and generalized estimating equations were used for outcomes assessment. **Results:** There were no significant between-group differences in length of stay or mortality. The Enterprise group had significantly lower odds of UIA-related inpatient readmissions versus the Neuroform/LVIS group (odds ratio: 0.62; 95% CI: 0.42–0.91). **Conclusion:** Enterprise stent use was associated with significantly lower readmissions versus competitor stent, with no difference in other study outcomes.

First draft submitted: 15 September 2020; Accepted for publication: 14 December 2020; Published online: 17 February 2021

Keywords: comparative effectiveness research • medical devices • neurology • observational research • real-world evidence

The prevalence of unruptured intracranial aneurysm (UIA) is estimated to be around 3.2% among middle-aged individuals [1,2], with rupture occurring in approximately a third of patients during their lifetime [3]. Endovascular coiling for UIA is associated with lower rates of disability and procedural complications compared with microsurgical clipping [4]. Yet, coiling alone is generally insufficient for the treatment of wide-necked aneurysms, which have a neck diameter of 4 mm or more or dome to neck ratio of less than 2, and are typically associated with high rates of complications and recurrence [5–7]. The advent of stent-assisted coiling, which prevents coil prolapse in the parent artery and promotes aneurysm thrombosis, has improved endovascular treatment of wide-necked aneurysms in recent years [8]. Several stent options are currently available and have been investigated in single-center, single-arm studies, with fewer studies performing direct comparisons of stent utility or effectiveness. Accordingly, there is a dearth of evidence regarding the specific benefits and disadvantages associated with available stent types to support clinical decision-making.

The Enterprise stent (CERENOVUS, CA, USA) has a closed-cell design that offers the ability to partially deploy, recapture and redeploy the stent for improved treatment of wide-necked aneurysms [8]. Two major alternatives to the Enterprise stent are the Neuroform stent system (Stryker Neurovascular, MI, USA) and the Low-profile Visualized Intraluminal Support (LVIS; MicroVention, CA, USA) stent. The Enterprise stent is a laser-cut nitinol stent with a tubular mesh structure, while the Neuroform stent is a laser-cut nitinol stent with an open-cell design. The LVIS stent is a braided self-expanding nitinol stent with a closed-cell implant [9]. These stents also differ in terms of

Future Medicine

available sizes, pore density, metal coverage, average loading force, passage force and deployment force [9], all of which could potentially lead to differences in patient outcomes.

Enterprise, Neuroform and LVIS are three of the most commonly used commercially available stents for UIA treatment. Studies have compared outcomes among patients with aneurysm undergoing stent-assisted coiling using the Enterprise stent versus Neuroform or LVIS stent [8,10–12]. However, results from these studies have been mixed, and limited in generalizability. This study aimed to utilize a nationally representative hospital billing dataset to perform a retrospective cohort analysis comparing the Enterprise stent to the Neuroform and LVIS stents in terms of real-world clinical and economic outcomes after accounting for patient demographics and co-morbidity, procedural and provider characteristics. LVIS is relatively new to the market but has established a strong market presence, as such we combined the Neuroform and LVIS together as the study comparator to establish adequate sample size for analyses. Our intent was to examine the performance of Enterprise stent in a pragmatic setting in comparison to its main alternatives. As such, our comparator group for the study included the two stents, Neuroform and LVIS, that are representative of the typical clinical scenario.

Methods

Data source

This study utilized hospital billing records contained in the Premier Healthcare Database (PHD) [13]. The PHD contains clinical coding, hospital cost and patient billing data from more than 700 hospitals throughout the United States. Although the database excludes federally funded hospitals (e.g., Veterans Affairs), the hospitals included are nationally representative based on bed size, geographic region, location (urban/rural) and teaching hospital status. The database contains a date-stamped log of all billed items by cost-accounting department including medications; laboratory, diagnostic and therapeutic services; and primary and secondary diagnoses for each patient's hospitalization. Identifier-linked enrollment files provide demographic and payor information. Detailed service-level information for each hospital day is recorded, including details about medications and devices.

The use of PHD for retrospective analyses, as conducted in this study, is considered exempt from Institutional Review Board (IRB) oversight as listed under Title 45 Code of Federal Regulations, Part 46 of the USA, specifically 45 CFR 46.101(b)(4) (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html).

Study population

We performed a retrospective cohort analysis of hospital-level data from the PHD for patients who underwent an elective inpatient endovascular coiling procedure with a primary diagnosis of UIA between 1 January 2011 and 31 December 2018. Eligible patients were aged ≥18 years or older at the time of index hospital admission (i.e., first observed inpatient hospital admission). Patients who had their index endovascular procedure at hospitals that did not continuously provide data to PHD in the 12-month preindex period were excluded. Other exclusion criteria were patients with a diagnosis of subarachnoid hemorrhage (SAH) or ruptured aneurysm; those who underwent an inpatient endovascular coiling or surgical clipping procedure for a primary or secondary diagnosis of UIA or SAH during the 12 months preceding the index date (i.e., preindex period); and patients who underwent an endovascular coiling procedure using any stent other than Enterprise, Neuroform and LVIS, or used more than one study stent.

Study covariates

Patient & procedural characteristics

Patient characteristics including age (18–49, 50–59, 60–69, ≥70 years), sex (male, female), race (white, nonwhite), marital status (married, single, other) and payer type (commercial, Medicare or Medicaid, other) were collected for the date of index hospitalization. Co-morbidities were assessed using Charlson Comorbidity Index (CCI) scores [14]. The CCI is an aggregate measure of co-morbidity that combines 19 select diagnoses associated with chronic disease (e.g., heart disease, cancer) weighted on a scale from +1 to +6. Higher scores are indicative of greater co-morbidity burden. We also noted and controlled for specific co-morbidities including diabetes, hypertension, polycystic kidney disease, congestive heart failure, peripheral vascular disorder, chronic pulmonary disease, ischemic stroke/transient ischemic attack (TIA), hypothyroidism, obesity and depression.

Provider characteristics

We recorded hospital characteristics including teaching status (teaching/nonteaching), geographic location (Midwest, Northeast, South, West), size (<300, 300–399, 400–499 and ≥500 beds), urban–rural classification and volume of endovascular coil procedures for UIA (using a median split) in the 12-month preindex period.

Study outcomes

Primary outcomes included short-term effectiveness measures including discharge status (defined in terms of mortality: died/alive) and length of stay (LOS) for the index admission, and long-term effectiveness measure including 12-month inpatient readmission (all-cause, cardiovascular [CV]-related, UIA-related, SAH-related). The 12-month total inpatient costs (sum of index admission cost and 12-month inpatient readmission cost) was also assessed. All costs were adjusted for medical inflation and are reported in 2018 US$. Cost data are from the perspective of hospital, and include room and board cost, laboratory cost, pharmacy cost, surgery cost, supply cost and other hospital cost components. The secondary outcome was complication rate including ischemic (aphasia, hemiplegia or cerebral artery occlusion), hemorrhagic (SAH or intracerebral hemorrhage), neurologic and other surgical complications (including ventriculostomy, ventriculoperitoneal shunt surgery or tracheostomy). Outcome measures were compared between the Enterprise stent group and Neuroform/LVIS (comparator) stent group.

Statistical analysis

All study variables are summarized as the mean and standard deviation for continuous variables and the frequency and percentage for categorical variables. Bivariate statistical tests (Chi square tests for categorical variables and t-tests for continuous variable comparison) were conducted to examine and describe between-group differences in potential confounding factors such as patient demographics, clinical characteristics, procedural characteristics and provider characteristics.

Propensity score matching was used to match patients in the Enterprise stent group with those in the comparison group based on study covariates. Patients were matched 1:1 using the GREEDY match nearest neighbor technique without replacement, enforcing a caliper of 0.10. Postmatch balance of covariates was examined using standardized mean differences (SMDs): a SMD ≥0.10 or ≤-0.10 was used to indicate good balance. SMDs were used as opposed to Chi square coefficients as the former provide covariate balance information independent of sample size. We performed two different propensity matching procedures: to compare outcomes associated with index admission (i.e., LOS, discharge status and complications), propensity matching was performed on the entire prematch sample identified based on study eligibility criteria; for outcomes based on 12-month follow-up assessment (i.e., 12-month all-cause, CV-related and UIA-related inpatient readmission, and total admission cost [sum of index admission and 12-month all-cause inpatient readmissions]), patients were only matched if they had index admission at hospitals that continuously provided data to the PHD for 12 months after the index hospital admission.

Bivariate analyses were conducted using student's *t*-test or Chi square/Fisher's exact test. Generalized estimating equation (GEE) models with an exchangeable correlation structure and appropriate link (logit link for discharge status, complications and readmission comparison; log link for LOS and cost comparison) and distribution function (binomial distribution for discharge status, complications, and readmission; negative binomial distribution for LOS; gamma distribution for cost) were utilized to compare outcomes between the study groups. GEE analyses adjusted comparisons for hospital clustering and any covariate that emerged significant postmatching (i.e., SMD ≥0.10 or ≤-0.10). All analyses were conducted using SAS ver. 9.4.

Results

Patient & provider characteristics

The sequence of patient enrollment is shown in Figure 1. The unmatched cohort included 1659 patients (616 Enterprise stent and 1043 comparator stent [782 Neuroform stent and 261 LVIS stent]). In this cohort, the Enterprise and comparator groups differed significantly in terms of marital status (marital status other 5.36 vs 11.22%, SMD = -0.2138), payor status (Medicaid 6.01 vs 11.51%, SMD = -0.1955), bed size (number of beds 400–499, 18.67 vs 14.00%, SMD = 0.1266), hospital geographic location (South 63.80 vs 58.10%, SMD = 0.117; West 5.19 vs 13.81%, SMD = -0.2969), hospital teaching status (teaching hospital 74.84 vs 32.50%, SMD = 0.1626), and co-morbidities. Most notable was a higher proportion of CCI scores 2–3 in the Enterprise versus comparator stent groups (71.6 vs 63.7%, SMD = 0.1701) and higher prevalence of specific co-morbidities including peripheral vascular disease (71.4 vs 57.1%, SMD = 0.3015), and depression (17.4 vs 13.0%, SMD = 0.1208) in the Enterprise

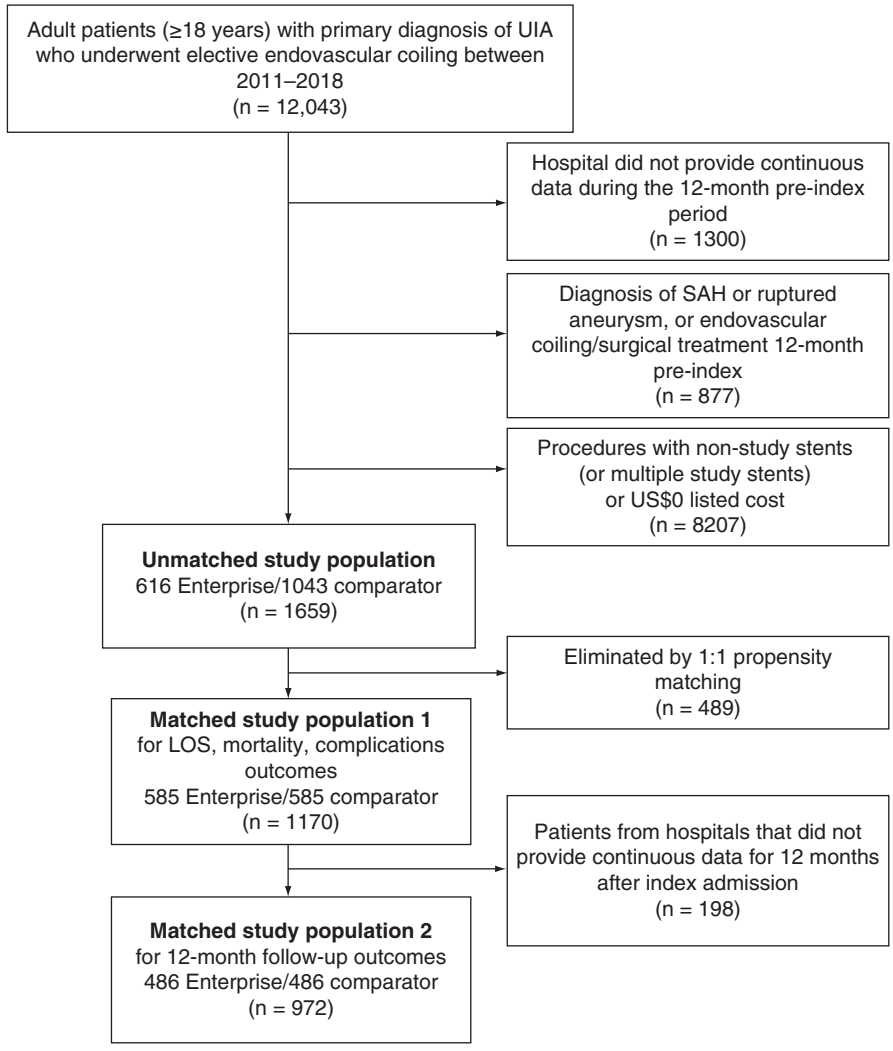

Figure 1. Attrition flow for study sample.
LOS: Length of stay; SAH: Subarachnoid hemorrhage; UIA: Unruptured intracranial aneurysm.

versus comparator stent groups. A total of 585 patient pairs were propensity matched (585 Enterprise stent vs [465 Neuroform stent + 120 LVIS stent]) for outcome comparison. Examination of SMDs revealed a perfect balance of covariates among the matched cohort, with no significant differences observed for any of the covariates. Table 1 lists the sample size and SMDs for the two cohorts by study covariates before and after matching.

When considering only patients from hospitals that provided continuous data during the 12 months after index hospital admission, 486 patients were matched to each group (Table 2). Examination of SMDs for the matched cohort depicted a good balance, with a significant difference observed only for the 'year' variable post-matching. Accordingly, GEE models comparing 12-month readmission and costs of care were adjusted for calendar 'year' in addition to hospital-level clustering.

Primary outcomes

Bivariate and adjusted analyses of discharge status defined in terms of mortality and LOS were conducted on the propensity-matched cohort (n = 585 per group) to compare the Enterprise and comparator (Neuroform/LVIS) stent groups. Discharge status did not significantly differ between groups in either analysis (Enterprise vs comparator, 1.0 vs 0.5%, p = 0.51; adjusted ratio of the mean, 1.98, 95% CI: 0.48–8.07). In contrast, LOS was significantly shorter in the Enterprise group compared with the comparator group in the bivariate analysis (1.89 ± 2.07 vs

Table 1. Sample characteristics and standardized mean differences before and after matching in the index admission outcome cohort.

Characteristic	Group	Pre-matching			Post-matching		
		Enterprise stent n = 616	Neuroform/LVIS n = 1043	SMD	Enterprise stent n = 585	Neuroform/LVIS n = 585	SMD
Age category	18–49	123 (19.97%)	172 (16.49%)	0.0901	116 (19.83%)	111 (18.97%)	0.0216
	50–59	151 (24.51%)	287 (27.52%)	-0.0685	146 (24.96%)	142 (24.27%)	0.0159
	60–69	196 (31.82%)	343 (32.89%)	-0.0228	187 (31.97%)	191 (32.65%)	-0.0146
	70+	146 (23.70%)	241 (23.11%)	0.0141	136 (23.25%)	141 (24.10%)	-0.0201
Sex	Male	144 (23.38%)	267 (25.60%)	-0.0517	136 (23.25%)	141 (24.10%)	-0.0201
Marital status	Married	328 (53.25%)	511 (48.99%)	0.0852	308 (52.65%)	299 (51.11%)	0.0308
	Single	255 (41.40%)	415 (39.39%)	0.0327	244 (41.71%)	257 (43.93%)	-0.0449
	Other	33 (5.36%)	117 (11.22%)	-0.2138	33 (5.64%)	29 (4.96%)	0.0305
Payor category	Commercial	255 (41.40%)	394 (37.78%)	0.0741	237 (40.51%)	227 (38.80%)	0.0349
	Medicaid	37 (6.01%)	120 (11.51%)	-0.1955	37 (6.32%)	31 (5.30%)	0.0438
	Medicare	279 (45.29%)	462 (44.30%)	0.0200	267 (45.64%)	283 (48.38%)	-0.0548
	Other	45 (7.31%)	67 (6.42%)	0.0349	44 (7.52%)	44 (7.52%)	0.0000
Race	White	474 (76.95%)	787 (75.46%)	0.0351	448 (76.58%)	448 (76.58%)	0.0000
Hospital bed size	≤299	57 (9.25%)	90 (8.63%)	0.0219	49 (8.38%)	50 (8.55%)	-0.0061
	300–399	38 (6.17%)	78 (7.48%)	-0.052	38 (6.50%)	30 (5.13%)	0.0585
	400–499	115 (18.67%)	146 (14.00%)	0.1266	112 (19.15%)	106 (18.12%)	0.0263
	≥500	406 (65.91%)	729 (69.89%)	-0.0854	386 (65.98%)	399 (68.21%)	-0.0473
Hospital region	Midwest	75 (12.18%)	132 (12.66%)	-0.0146	75 (12.82%)	74 (12.65%)	0.0051
	Northeast	116 (18.83%)	161 (15.44%)	0.0902	104 (17.78%)	103 (17.61%)	0.0045
	South	393 (63.80%)	606 (58.10%)	0.117	374 (63.93%)	379 (64.79%)	-0.0178
	West	32 (5.19%)	144 (13.81%)	-0.2969	32 (5.47%)	29 (4.96%)	0.0231
Hospital teaching status	Teaching	461 (74.84%)	339 (32.50%)	0.1626	435 (74.36%)	433 (74.02%)	0.0078
Urban–rural location	Urban	598 (97.08%)	1,026 (98.37%)	-0.0867	571 (97.61%)	572 (97.78%)	-0.0114
Endovascular coiling volume (median split)	Above median	332 (53.90%)	513 (49.19%)	0.0944	311 (53.16%)	317 (54.19%)	-0.0206
Year	2011	109 (17.69%)	98 (9.40%)	0.2443	101 (17.26%)	85 (14.53%)	0.0749
	2012	99 (16.07%)	121 (11.60%)	0.1297	93 (15.90%)	93 (15.90%)	0.0000
	2013	87 (14.12%)	134 (12.85%)	0.0374	84 (14.36%)	89 (15.21%)	-0.0241
	2014	79 (12.82%)	98 (9.40%)	0.1093	71 (12.14%)	73 (12.48%)	-0.0104
	2015	71 (11.53%)	146 (14.00%)	-0.0741	71 (12.14%)	70 (11.97%)	0.0053
	2016	89 (14.45%)	159 (15.24%)	-0.0224	84 (14.36%)	93 (15.90%)	-0.0429
	2017	58 (9.42%)	144 (13.81%)	-0.1374	57 (9.74%)	61 (10.43%)	-0.0227
	2018	24 (3.90%)	143 (13.71%)	-0.3517	24 (4.10%)	21 (3.59%)	0.0267
CCI	Score 1	111 (18.02%)	264 (25.31%)	-0.1777	107 (18.29%)	112 (19.15%)	-0.0219
	Score 2–3	441 (71.59%)	664 (63.66%)	0.1701	417 (71.28%)	416 (71.11%)	0.0038
	Score ≥4	64 (10.39%)	115 (11.03%)	-0.0206	61 (10.43%)	57 (9.74%)	0.0227
Co-morbidities	Heart failure	18 (2.92%)	29 (278%)	0.0085	17 (2.91%)	15 (2.56%)	0.0210
	Diabetes	84 (13.64%)	158 (15.15%)	-0.0431	81 (13.85%)	70 (11.97%)	0.0561
	Hypertension	395 (64.12%)	705 (67.59%)	-0.0732	373 (63.76%)	390 (66.67%)	-0.0610
	Stroke/TIA	81 (13.15%)	104 (9.97%)	0.0995	70 (11.97%)	70 (11.97%)	0.0000
	Peripheral vascular disease	440 (71.43%)	596 (57.14%)	0.3015	415 (70.94%)	408 (69.74%)	0.0262
	Chronic pulmonary disease	118 (19.16%)	204 (19.56%)	-0.0102	109 (18.63%)	108 (18.46%)	0.0044
	Hypothyroidism	78 (12.66%)	127 (12.18%)	0.0147	73 (12.48%)	75 (12.82%)	-0.0103
	Obesity	72 (11.69%)	106 (10.16%)	0.0489	69 (11.79%)	64 (10.94%)	0.0269
	Depression	107 (17.37%)	136 (13.04%)	0.1208	98 (16.75%)	87 (14.87%)	0.0516

CCI: Charlson comorbidity index; LVIS: Low-profile visualized intraluminal support; SMD: Standard mean difference; TIA: Transient ischemic attack.

Table 2. Sample characteristics and standardized mean differences before and after matching in the 12-month outcome cohort.

Characteristic	Group	Pre-matching			Post-matching		
		Enterprise stent n = 514	Neuroform/LVIS n = 781	SMD	Enterprise stent n = 486	Neuroform/LVIS n = 486	SMD
Age category	18–49	104 (20.23%)	136 (17.41%)	0.0722	97 (19.96%)	95 (19.55%)	0.0103
	50–59	123 (23.93%)	222 (28.43%)	-0.1024	120 (24.69%)	114 (23.46%)	0.0289
	60–69	166 (32.30%)	252 (32.27%)	0.0006	155 (31.89%)	160 (32.92%)	-0.022
	70+	121 (23.54%)	171 (21.90%)	0.0393	114 (23.46%)	117 (24.07%)	-0.0145
Sex	Male	121 (23.54%)	190 (24.33%)	-0.0184	120 (24.69%)	111 (22.84%)	0.0435
Marital status	Married	280 (54.47%)	369 (47.25%)	0.145	262 (53.91%)	252 (51.85%)	0.0412
	Single	215 (41.83%)	323 (41.36%)	0.0096	205 (42.18%)	212 (43.62%)	-0.0291
	Other	19 (3.70%)	89 (11.40%)	-0.2946	19 (3.91%)	22 (4.53%)	-0.0307
Payor category	Commercial	212 (41.25%)	297 (38.03%)	0.0658	197 (40.53%)	191 (39.30%)	0.0252
	Medicaid	29 (5.64%)	90 (11.52%)	-0.2111	29 (5.97%)	26 (5.35%)	0.0267
	Medicare	236 (45.91%)	343 (43.92%)	0.0401	224 (46.09%)	232 (47.74%)	-0.033
	Other	37 (7.20%)	51 (6.53%)	0.0264	36 (7.41%)	37 (7.61%)	-0.0078
Race	White	401 (78.02%)	589 (75.42%)	0.0615	379 (77.98%)	377 (77.57%)	0.0099
Hospital bed size	≤299	34 (6.61%)	57 (7.30%)	-0.0269	33 (6.79%)	32 (6.58%)	0.0082
	300–399	32 (6.23%)	57 (7.30%)	-0.0427	29 (5.97%)	35 (7.20%)	-0.0498
	400–499	92 (17.90%)	96 (12.29%)	0.1571	83 (17.08%)	79 (16.26%)	0.0221
	≥500	356 (69.26%)	571 (73.11%)	-0.0851	341 (70.16%)	340 (69.96%)	0.0045
Hospital region	Midwest	64 (12.45%)	91 (11.65%)	0.0246	61 (12.55%)	62 (12.76%)	-0.0062
	Northeast	78 (15.18%)	115 (14.72%)	0.0126	73 (15.02%)	68 (13.99%)	0.0292
	South	351 (68.29%)	480 (61.46%)	0.1434	331 (68.11%)	336 (69.14%)	-0.0222
	West	21 (4.09%)	95 (12.16%)	-0.299	21 (4.32%)	20 (4.12%)	0.0102
Hospital teaching status	Teaching	373 (72.57%)	518 (66.33%)	0.1358	350 (72.02%)	344 (70.78%)	0.0273
Urban–rural location	Urban	496 (96.50%)	766 (98.08%)	-0.0975	469 (96.50%)	472 (97.12%)	-0.0351
Endovascular coiling volume (median split)	Above median	276 (53.70%)	377 (48.27%)	0.1087	257 (52.88%)	260 (53.50%)	-0.0124
Year	2011	94 (18.29%)	72 (9.22%)	0.2656	86 (17.70%)	65 (13.37%)	0.1195
	2012	82 (15.95%)	112 (14.34%)	0.045	77 (15.84%)	81 (16.67%)	-0.0223
	2013	78 (15.18%)	124 (15.88%)	-0.0194	75 (15.43%)	75 (15.43%)	0
	2014	78 (15.18%)	91 (11.65%)	0.1035	70 (14.40%)	70 (14.40%)	0
	2015	68 (13.23%)	129 (16.52%)	-0.0925	66 (13.58%)	71 (14.61%)	-0.0296
	2016	77 (14.98%)	125 (16.01%)	-0.0283	75 (15.43%)	70 (14.40%)	0.0289
	2017	34 (6.61%)	104 (13.32%)	-0.2251	34 (7.00%)	38 (7.82%)	-0.0314
	2018	–	–	–	–	–	–
CCI	Score 1	77 (14.98%)	155 (19.85%)	-0.1286	76 (15.64%)	76 (15.64%)	0
	Score 2–3	379 (73.74%)	541 (69.27%)	0.099	354 (72.84%)	360 (74.07%)	-0.028
	Score ≥4	58 (11.28%)	85 (10.88%)	0.0128	56 (11.52%)	50 (10.29%)	0.0396
Co-morbidities	Heart failure	17 (3.31%)	18 (2.30%)	0.0607	15 (3.09%)	16 (3.29%)	-0.0117
	Diabetes	66 (12.84%)	121 (15.49%)	-0.0761	64 (13.17%)	71 (14.61%)	-0.0417
	Hypertension	329 (64.01%)	519 (66.45%)	-0.0514	314 (64.61%)	319 (65.64%)	-0.0216
	Stroke/TIA	62 (12.06%)	69 (8.83%)	0.1057	55 (11.32%)	52 (10.70%)	0.0197
	Peripheral vascular disease	392 (76.26%)	515 (65.94%)	0.2292	366 (75.31%)	365 (75.10%)	0.0048
	Chronic pulmonary disease	101 (19.65%)	161 (20.61%)	-0.0241	97 (19.96%)	93 (19.14%)	0.0208
	Hypothyroidism	62 (12.06%)	92 (11.78%)	0.0087	56 (11.52%)	56 (11.52%)	0
	Obesity	60 (11.67%)	84 (10.76%)	0.0291	54 (11.11%)	53 (10.91%)	0.0066
	Depression	86 (16.73%)	99 (12.68%)	0.1147	81 (16.67%)	73 (15.02%)	0.0451

CCI: Charlson comorbidity index; LVIS: Low-profile visualized intraluminal support; SMD: Standard mean difference; TIA: Transient ischemic attack.

Table 3. Rates of 12-month inpatient readmission between Enterprise and comparator stents.

Readmission	Bivariate comparison (enterprise vs comparator), %	p-value	Odds ratio (GEE model)	95% CI
All-cause readmission	21.19 vs 27.57	**0.0206**‡	**0.72**	**0.53–0.97**
CV-related readmission	14.81 vs 20.58	**0.0186**‡	**0.70**	**0.50–0.97**
UIA-related readmission	10.08 vs 15.64	**0.0097**‡	**0.62**	**0.42–0.91**
SAH-related readmission	0.21 vs 0.00	1.000†	–	–

A total of 486 patients were matched per group for outcome analysis. Regression models were adjusted for year (significant covariate in matched sample). Statistical significance is indicated in bold.
†p-value based on Fisher's Exact test.
‡p-value based on χ^2 test.
CV: Cardiovascular; GEE: Generalized estimating equation; SAH: Subarachnoid hemorrhage; UIA: Unruptured intracranial aneurysm.

Table 4. Twelve-month costs of care for index admission and inpatient readmission between the Enterprise and comparator stent groups.

Admission	Bivariate comparison (enterprise vs comparator), US$	p-value	Adjusted ratio of the mean (GEE model)	95% CI
Index admission	34,072 (±16,164) vs 35,828 (±21,087)	**<0.0001**	0.95	0.88–1.03
Index admission + all-cause readmission	104,667 (±235,968) vs 126,796 (±271,971)	**0.0018**	0.83	0.62–1.10
Index admission + CV-related readmission	38,466 (±20,876) vs 42,784 (±25,090)	**<0.0001**	0.91	0.82–1.00
Index admission + UIA-related readmission	37,638 (±20,156) vs 41,427 (±24,029)	**0.0001**	0.92	0.84–1.01

A total of 486 patients were matched per group for outcome analysis. Bivariate data are reported as the mean and standard deviation. Regression models were adjusted for calendar year (significant covariate in matched sample). Statistical significance is indicated in bold.
CV: Cardiovascular; GEE: Generalized estimating equation; UIA: Unruptured intracranial aneurysm.

2.11 ± 2.81, $p < 0.0001$), but did not emerge to be statistically significantly different in GEE analysis (adjusted ratio of the mean, 0.90, 95% CI: 0.73–1.10).

Analyses of 12-month follow-up outcomes were conducted on a cohort of propensity-matched patients from hospitals that continuously provided data to the PHD for 12 months after the index hospital admission (n = 486 per group). With regard to inpatient readmission, the Enterprise group exhibited lower rates of all-cause (21.2 vs 27.6%, p = 0.021), CV-related (14.8 vs 20.6%, p = 0.019) and UIA-related readmission (10.1 vs 15.6%, p = 0.010) compared with the comparator group in the bivariate analysis. Statistical significance was preserved after adjustment in the GEE analysis: Enterprise stent patients had 28% lower odds of 12-month all-cause inpatient readmission (OR: 0.72; 95% CI: 0.53–0.97), 30% lower odds of 12-month CV-related readmission (OR: 0.70; 95% CI: 0.50–0.97) and 38% lower odds of 12-month UIA-related readmission (OR: 0.62; 95% CI: 0.42–0.91; Table 3) compared with the comparator stent group.

Examining the cost of care, we found mean cost of index admission was significantly lower in the Enterprise group than the comparator group in the bivariate analysis (US$34,072 vs $35,828, $p < 0.001$); however, this difference was nonsignificant after adjustment (adjusted ratio of the mean, 0.95, 95% CI: 0.88–1.03). A similar trend was observed for total costs (index admission plus 12-month all-cause inpatient readmission), which were lower in the Enterprise group when considering all-cause readmission (US$104,667 vs $126,795, p = 0.002), CV-related readmission (US$38,466 vs $42,784, $p < 0.0001$), and UIA-related readmission (US$37,638 vs $41,427, p = 0.001), but not statistically significant after adjustment in the GEE model (Table 4).

Secondary outcomes

Bivariate analysis of complication rates between the Enterprise and comparator groups (n = 585) revealed no significant differences in the rates of total, ischemic, hemorrhagic, neurologic or other complications (Supplementary Table 1).

Discussion

Using a nationally representative multihospital database, this study compared key clinical and economic outcomes of endovascular treatment with the Enterprise stent versus its comparators, the Neuroform and LVIS stents. While there were no major differences in patient outcomes or complication rates between the stent groups, patients treated with Enterprise had 28–38% lower odds of all-cause, CV-related and UIA-related readmission compared with the

comparator group. In the bivariate analysis, this difference was associated with a corresponding lower cost; however, the cost benefit was not statistically significant after adjustment for hospital clustering in the GEE model.

Few studies have compared outcomes among patients with UIA undergoing stent-assisted coiling using the Enterprise stent versus the LVIS or Neuroform stent, and these studies have reported mixed results. When comparing outcomes among 190 patients treated for UIA with the Enterprise stent or LVIS stent, Ge *et al.* observed no significant between-group differences in clinical outcomes (modified Rankin Scale [mRS] score: 0–2; 90.9 vs 94.9%, p = 0.379) or procedure-related complications (16.3 vs 10.9%, p = 0.298) [10]. Although the authors reported significantly higher rates of complete or near-complete occlusion in the LVIS group versus the Enterprise stent group (96.9 vs 88.4%, p = 0.048), this difference did not adjust for variation in patient clinical characteristics including aneurysm size, morphology and location. In another study by Kadkhodayan *et al.* comparing aneurysms treated with the Enterprise stent (98 patients) and Neuroform stent (160 patients) using prospective registry data, the Enterprise stent was associated with a statistically superior deployment rate (difficult deployment rate, 1.7 vs 15.9%, p < 0.0001) and occlusion rate (87.3 vs 73.0%, p = 0.0058) [8]. The authors reported no significant difference in hemorrhagic complications between the two groups; however, thromboembolic complications were higher for Enterprise stent patients compared with Neuroform patients (8.7 vs 1.4%, p = 0.0021). In a single-center study of 130 aneurysm patients treated with Enterprise stent and Neuroform stent, Durst *et al.* found that use of the Neuroform stent was a predictor for retreatment (p = 0.034), but did not observe any difference in occlusion rates between the two groups [11]. In another single-center study comparing the Enterprise, Neuroform, and LVIS (including LVIS Jr) stents, Wang *et al.* reported all three stents to be safe and effective for the treatment of cerebral aneurysms, with some variation seen in terms of initial complete occlusion, progressive occlusion and complication rates among the three groups [12].

Though the above studies provide useful information, the generalizability of their findings is limited by the single-center nature of these studies together with a lack of adjustment for patient characteristics in outcome assessments. A more recent study by Mokin *et al.* (2019) compared outcomes among 659 aneurysm patients undergoing endovascular coiling using Enterprise, Neuroform, and LVIS stents across multiple centers [15]. In unadjusted bivariate analyses, the results from the study indicated LVIS (including LVIS Jr.) group to have the highest rate of complete occlusion (RRGS 1) at baseline (64.4 vs 47.6 vs 56.2%; p = 0.008) and follow-up (83.9 vs 67.5 vs 78%; p = 0.004) as compared with Enterprise and Neuroform group. However, in multivariate adjustment, no significant difference in complete occlusion at baseline (p = 0.098) and follow-up (p = 0.113) was observed by type of stent in the study [15], reflecting that the significant differences observed in their bivariate analyses dissipates when adjusted for study covariates. Though these reports provide useful information, the results are difficult to generalize to a real-world setting given important limitations in study design including limited sample and largely single-center or few center experience, along with the fact that these studies did not adjust statistical comparisons for important patient and provider characteristics known to influence outcome.

In our study, we did not observe any significant difference in discharge status among patients who underwent endovascular treatment using the Enterprise stent versus comparator group stents. From bivariate comparison, patients in the Enterprise stent group did appear to have shorter LOS compared with the comparator group, though this difference was not significant when adjusting for hospital clustering.

Readmissions is a key marker of long-term treatment effectiveness when considering secondary data sources such as the PHD, which do not include tailored study end point variables; however, readmissions for cardiovascular and UIA reasons are a clinically important measure of success for patients and healthcare providers. Specifically, UIA-related readmissions could represent a differential in retreatment procedures being performed across the study devices. Patients in the Enterprise stent group had significantly lower rates of readmission compared with the Neuroform or LVIS comparator group. The approximately 38% lower likelihood of UIA-related readmission in the subsequent 12-month period postendovascular procedure for Enterprise stent patients versus the comparator group may reflect a clinical benefit accrued with the use of Enterprise stent. Our results are consistent with the finding of Durst *et al.* identifying use of Neuroform stent as a predictor of retreatment (compared with Enterprise stent) [9]. The authors alluded to differences in stent design, specifically to Neuroform's open-cell design and an associated increased potential for coil herniation, as a likely cause of higher retreatment rates in the Neuroform group. It should be acknowledged that our comparator group included patients who underwent procedures using either the Neuroform stent or LVIS stent, unlike Durst *et al.* [9], who directly compared the Neuroform stent to the Enterprise stent. Further research is needed to understand individual differences when comparing use of the Enterprise stent versus Neuroform stent, and the Enterprise stent versus LVIS stent, in a real-world setting.

As healthcare dollars are increasingly scrutinized, it is important to understand cost differences associated with device selection from both a payer and provider perspective. Our results showed that endovascular procedure costs were US$1756 lower in the Enterprise stent group versus the comparator stent group. When examining the total cost of care, calculated as the sum of index endovascular procedure costs and 12-month all-cause inpatient admission costs, Enterprise stent use was associated with a cost savings of US$22,129 compared with the comparator stents. When limiting the total cost of care to include only the index procedure and 12-month UIA-related readmission costs, this cost difference was US$3789 in favor of the Enterprise stent group. Notably, these differences approached significance in the GEE model. These results indicate a potential economic benefit associated with use of the Enterprise stent versus the Neuroform or LVIS stents.

It is important to note that the population of patients who underwent endovascular treatment with the Enterprise stent in the PHD generally had higher rates of specific co-morbidities such as stroke/TIA, peripheral vascular disease and depression as well as higher CCI scores compared with the comparator group before matching. Further research is needed to better understand the underlying reason (if any) for this difference in patient clinical profiles between the two groups, especially the observation of higher co-morbidity burden among patients treated with the Enterprise stent.

This study had a few limitations. Though we used a robust analytical technique that implemented propensity matching, unmeasured confounders could have influenced the study results. In the PHD, readmission is only captured if the patient returns to the same hospital and not if the patient is readmitted to another hospital (irrespective of whether that hospital contributes data to the PHD or not). As a result, the rates of readmission observed in our study could underestimate true rates of readmission among patients undergoing endovascular procedures. Given the lack of differential coding for wide-necked aneurysms, we were unable to ascertain the proportion of such patients in our study. Also important, due to limitations in the data and patient volume we included multiple generations of both the Neuroform and LVIS stents in our comparator group; further research is needed to understand the differences between outcomes associated with Enterprise and each of these respective competitor stents. Moreover, as medical device features evolve, it would be important to study differences among the latest version of these devices. For example, the Enterprise 2 stent was designed to have an improved vessel wall conformability, with one study reporting the gap between vessel wall and stent for Enterprise 2 stent to be half of the gap observed for the first generation of Enterprise stent [16]. Similarly, multiple generations of the Neuroform device have been launched over the years ever since the device was first approved in 2002 [17]. The most recent version of this device, in other words, the Neuroform Atlas has been said to have lower profile delivery, better scaffolding, improved trackability and higher conformability as compared with prior generations of the device [17]. As with LVIS, there are multiple generations including LVIS and LVIS Jr, with the latter designed to allow deployment to smaller and more tortuous vessels [18]. As more data become available for the three study devices, researchers could perform a comparative analysis focused on these recent versions. Lastly, coding errors during claims processing could have influenced the study results.

Conclusion

To the best of our knowledge, this is the first study to compare outcomes that assess the effectiveness of UIA treatment among patients who underwent endovascular coiling procedures with the Enterprise stent versus the Neuroform or LVIS stent in a real-world setting. Our results suggest that use of the Enterprise stent is associated with a significant decrease in hospital readmission for cardiovascular and UIA reasons and a similar safety profile compared with the Neuroform and LVIS stents. The results for LOS and cost outcomes were mixed, with results from bivariate analyses suggesting significantly lower LOS and cost (index admission and total cost) among Enterprise stent patients as compared with competitor stent, while the results from GEE for LOS and cost indicated no significant difference among the study cohorts. Further research is needed to examine if lower rates of inpatient admissions among Enterprise stent cohort translate into significant economic savings as compared with Neuroform/LVIS stents.

Summary points

- Stent-assisted coiling is increasingly being used for the endovascular treatment of wide-necked aneurysms in patients with unruptured intracranial aneurysms (UIA).
- Three of the most commonly used stents are Enterprise stent, Neuroform stent and Low-profile Visualized Intraluminal Support (LVIS) stent.
- Using the Premier Healthcare Database, which is a nationwide, hospital billing database in the United States, this study examined differences in length of stay, discharge status (mortality), 12-month inpatient admissions (all-cause, cardiovascular-related, UIA-related), cost and complications among UIA patients who underwent endovascular coiling using the Enterprise stent versus the Neuroform or LVIS stent.
- Propensity score matching was used to match patients in the two groups (Enterprise stent vs Neuroform/LVIS) on study covariates including patient demographics and comorbidity status, and provider characteristics, with outcomes examined in the matched cohort using generalized estimating equation.
- No significant difference in length of stay, discharge status and costs were observed between the study cohorts in generalized estimating equation analyses.
- The likelihood of 12-month inpatient admissions (all-cause, cardiovascular-related, UIA-related) were significantly lower for Enterprise stent patients as compared with Neuroform/LVIS patients.
- No significant differences in complications were observed among the two study cohorts.
- Endovascular coiling using Enterprise stent was associated with significantly lower rates of readmission as compared with Neuroform/LVIS stent use, which may translate to economic savings for patients, providers and payers.

Author contributions

All the authors contributed to the conception and design of the study. E Kottenmeier, SHY Lee and R Khanna were responsible for the collection and assembly of data, and data analysis and interpretation. All the authors were responsible for the manuscript writing and final approval of the manuscript.

Financial & competing interests disclosure

This study was sponsored by Cerenovus. R De Leacy is on the scientific advisory board of Cerenovus, stroke advisory board/consultant of Siemens, consultant for Imperative Care, Penumbra and Medical Metrics and has equity in Q'Apel Medical, Synchron and Endostream. E Kottenmeier, SHY Lee and R Khanna are employees of Johnson and Johnson. AM Spiotta has consulting agreements with Penumbra, Cerenovus, Terumo and Stryker. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

The authors acknowledge Superior Medical Experts for manuscript editing services.

Ethical conduct of research

In the United States, retrospective analyses of the Premier Healthcare Database data are considered exempt from institutional review board (IRB) oversight as dictated by Title 45 Code of Federal Regulations, Part 46 of the USA, specifically 45 CFR 46.101(b)(4) (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html).

Data sharing statement

Data may be obtained from a third party and are not publicly available.

References

Papers of special note have been highlighted as: •• of considerable interest

1. Lasheras JC. The biomechanics of arterial aneurysms. *Annu. Rev. Fluid. Mech.* 39, 293–319 (2007).
2. Vlak MH, Algra A, Brandenburg R *et al.* Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis. *Lancet Neurol.* 10(7), 626–636 (2011).
3. Korja M, Lehto H, Juvela S. Lifelong rupture risk of intracranial aneurysms depends on risk factors: a prospective Finnish cohort study. *Stroke* 45(7), 1958–1963 (2014).
4. Li ZQ, Wang QH, Chen G *et al.* Outcomes of endovascular coiling versus surgical clipping in the treatment of ruptured intracranial aneurysms. *J. Int. Med. Res.* 40(6), 2145–2151 (2012).
5. Cognard C, Weill A, Spelle L *et al.* Long-term angiographic follow-up of 169 intracranial berry aneurysms occluded with detachable coils. *Radiology* 212(2), 348–356 (1999).

6. Fernandez Zubillaga A, Guglielmi G, Vinuela F *et al.* Endovascular occlusion of intracranial aneurysms with electrically detachable coils: correlation of aneurysm neck size and treatment results. *Am. J. Neuroradiol.* 15(5), 815–820 (1994).
7. Murayama Y, Nien YL, Duckwiler G *et al.* Guglielmi detachable coil embolization of cerebral aneurysms: 11 years' experience. *J. Neurosurg.* 98(5), 959–966 (2003).
8. Kadkhodayan Y, Rhodes N, Blackburn S *et al.* Comparison of Enterprise with Neuroform stent-assisted coiling of intracranial aneurysms. *Am. J. Roentgenol.* 200(4), 872–878 (2013).

•• **Enterprise stent use was associated with statistically significant superior deployment rate and occlusion rate as compared with Neuroform stent.**

9. Cho SH, Jo WI, Jo YE *et al.* Bench-top comparison of physical properties of 4 commercially-available self-expanding intracranial stents. *Neurointervention* 12(1), 31–39 (2017).
10. Ge H, Lv X, Yang X *et al.* LVIS stent versus Enterprise stent for the treatment of unruptured intracranial aneurysms. *World Neurosurg.* 91, 365–370 (2016).

•• **Showed no significant difference in modified Rankin Scale score and procedural complications between Enterprise stent and Low-profile Visualized Intraluminal Support stent among unruptured intracranial aneurysms patients.**

11. Durst CR, Khan P, Gaughen J *et al.* Direct comparison of Neuroform and Enterprise stents in the treatment of wide-necked intracranial aneurysms. *Clin. Radiol.* 69(12), 471–476 (2014).

•• **Neuroform stent was found to be a predictor of retreatment, with no difference observed in occlusion rate compared with Enterprise stent.**

12. Wang J, Vargas J, Spiotta A *et al.* Stent-assisted coiling of cerebral aneurysms: a single-center clinical and angiographic analysis. *J. Neurointerv. Surg.* 10(7), 687–692 (2018).
13. Premier Applied Sciences. Premier Healthcare Database White Paper: Data that Informs and Performs (2020). https://products.premierinc.com/downloads/PremierHealthcareDatabaseWhitepaper.pdf
14. de Groot V, Beckerman H, Lankhorst GJ *et al.* How to measure comorbidity: a critical review of available methods. *J. Clin. Epidemiol.* 56, 221–229 (2003).
15. Mokin M, Primiani CT, Ren Z *et al.* Stent-assisted coiling of cerebral aneurysms: multi-center analysis of radiographic and clinical outcomes in 659 patients. *J. Neurointerv. Surg.* 12(3), 289–297 (2020).
16. Kono K, Terada T. *In vitro* experiments of vessel wall apposition between the Enterprise and Enterprise 2 stents for treatment of cerebral aneurysms. *Acta Neurochirurgica* 158(2), 241–245 (2016).
17. Jankowitz BT, Hanel R, Jadhav AP *et al.* Neuroform Atlas Stent System for the treatment of intracranial aneurysm: primary results of the Atlas Humanitarian Device Exemption cohort. *J. Neurointerv. Surg.* 11(8), 801–806 (2019).
18. Gupta M, Cheung VJ, Abraham P *et al.* Low-profile visualized intraluminal support junior device for the treatment of intracranial aneurysms. *Cureus* 9, 2 (2017).