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Cost-Effectiveness Analysis of Encephaloduroarteriosynangiosis Surgery for Symptomatic Intracranial Atherosclerotic Disease

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Encephaloduroarteriosynangiosis (EDAS) is a promising treatment for cerebral arterial steno-occlusive disorders, with proven efficacy in moyamoya disease and a growing interest in potential application for patients with symptomatic intracranial atherosclerotic disease, given the early results of intermediate development trials showing reduced rates of recurrence stroke and improved clinical outcomes compared with those patients treated with intense medical management (IMM) alone. Although clinical outcomes are the fundamental goal when considering patient care paradigms, a cost-effective analysis is key to obtaining a comprehensive understanding of the impact EDAS may provide to patients with atherosclerotic disease on a larger scale. Here, we evaluate the EDAS + IMM cost-effectiveness over time in the treatment of intracranial atherosclerotic disease compared with IMM alone.

KEY WORDS: Cost-effectiveness, EDAS, Intracranial atherosclerosis, Stroke, Medical management, Indirect cerebral revascularization

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Recent evidence has positioned encephaloduroarteriosynangiosis (EDAS) as a promising treatment for patients with symptomatic intracranial atherosclerotic disease (ICAD).[1–5] ICAD is a complex stroke etiology associated with the highest recurrent rates of stroke and death, even when treated with best contemporary intensive medical management (IMM),[6,7] which translates in elevated patient care costs.[8] Other treatments such as angioplasty/stenting[6,9] and direct bypass[10,11] have not proven efficacy in randomized clinical trials and have also failed to show beneficial cost-effectiveness (CE).[12,13] Exploring the CE of EDAS is important in determining the applicability of this technique as a potential form of treatment for ICAD.

ABBREVIATIONS: ARR, absolute risk reduction; **CE,** cost-effectiveness; **EDAS,** encephaloduroarteriosynangiosis; **ERSIAS-PC,** encephaloduroarteriosynangiosis revascularization for symptomatic intracranial atherosclerotic steno-occlusive performance criterion; **ICAD,** intracranial atherosclerotic disease; **ICER,** incremental cost-effectiveness ratio; **IMM,** intense medical management; **QALY,** quality-adjusted life-year.

METHODS

To analyze the CE of EDAS plus best medical management (EDAS + IMM) compared with medical management alone (IMM), each intervention's costs were calculated as follows: The cost per individual initial treatment was calculated as the sum of procedure costs (EDAS + IMM or IMM alone) and the cost of initial hospital admission and workup. The cost of hospital readmission for any stroke during follow-up, the additional annual cost of disability for major (modified Rankin scale >3) stroke, and the cost of death were calculated using the data reported by Sun et al,[14] Engel-Nitz et al,[8] and Kahn et al,[12] extracted from the Healthcare Research and Quality Nationwide Inpatient Sample database,[15] and adjusted for inflation to 2021 US dollars, using the US Inflation Calculator[16] that uses the latest US Government Consumer Price Index data published in July 2021 by the US Labor Department's Bureau of Labor Statistics to adjust for inflation and calculate the cumulative inflation rate through June 2021. Quality-of-life scores for average health, major stroke, and minor stroke were obtained from published studies on stroke and poststroke quality of life.[12,17,18] Major stroke was defined as a modified Rankin scale score > 3. Quality-adjusted life-year (QALY) was estimated using the frequency of

TABLE 1. Base-Case Cost and Outcome Health Utilities

	Cost (2021 USD)
EDAS + IMM	$40 882.84
IMM	$20 968.00
Recurrent any stroke admission and follow-up	$40 038.50
Disability major stroke	$44 171.99
Death	$15 614.97
Baseline health[a]	**Utilities**
Minor stroke	0.89
Major stroke	0.64
Death	0.34
	0

EDAS, encephaloduroarteriosynangiosis; ICAD, intracranial atherosclerotic disease; IMM, intense medical management; USD, US dollars.
[a]Baseline health for patients with ICAD.[12,18]

disabling and nondisabling stroke, death, and baseline health observed in the EDAS Revascularization for Symptomatic Intracranial Atherosclerotic Steno Occlusive Performance Criterion (ERSIAS-PC) trial for ERSIAS + IMM (n = 52) and IMM alone (n = 52).[2] Table 1 summarizes the base-case cost and outcome health utility scores. Two analyses were conducted using these data: First, using the ERSIAS-PC trial observed absolute risk reduction (ARR)/year (5.8%) and rates of stroke (disabling and nondisabling) and death, outcomes from 1 to 4 years were calculated. Then, a more conservative range of ARR/year (2%-4%) was used to project a spectrum of CE for ARR/year that could be explored in randomized clinical trials.

Incremental CE ratio (ICER) was formulated from 1 to 4 years for the ARR of the ERSIAS-PC (5.8%) and for different ARRs (2%, 2.5%, 3%, 3.5%, and 4%). A threshold to accept an ICER as CE was determined using the World Health Organization recommendations for CE analysis,[19] which is an ICER below 3 times the gross domestic product per capita; for the United States, this threshold was calculated at US$150 000 in 2020.

RESULTS

The rates of stroke/death in ERSIAS-PC at 24 months were 9.6% in the EDAS + IMM group and 21.2% in the IMM group, which corresponds to an ARR/year of 5.8%. In the ERSIAS-PC trial, the yearly rates of any stroke, disabling

TABLE 2. QALY and Cost/QALY (per Group) and ICER for the Observed Results in the ERSIAS-PC Trial and Projected to Lower ARR/Year for a Multicenter Trial

	ARR (%/y)	Year	QALY EDAS + IMM	Cost/QALY – EDAS + IMM	QALY IMM	Cost/QALY – IMM	ICER
ERSIAS PC	5.8	1	0.87	$42 164.69	0.84	$26 255.05	$474 451.37
		2	0.85	$45 209.44	0.78	$34 315.23	$162 441.61
		3	0.83	$48 408.00	0.72	$43 580.02	$47 992.76
		4	0.80	$51 772.32	0.66	$54 341.28	−$19 152.65
Projected for different ARR	2	1	0.85	$52 618.88	0.84	$33 186.81	$1 121 498.82
	2	2	0.81	$60 107.58	0.78	$44 306.96	$455 957.17
	2	3	0.77	$68 365.71	0.72	$57 186.04	$215 073.77
	2	4	0.73	$77 518.25	0.66	$72 277.22	$75 619.97
	2.5	1	0.86	$52 227.58	0.84	$33 186.81	$975 941.52
	2.5	2	0.82	$59 249.05	0.78	$44 306.96	$382 931.07
	2.5	3	0.78	$66 946.57	0.72	$57 186.04	$166 759.76
	2.5	4	0.74	$75 422.71	0.66	$72 277.22	$40 305.81
	3	1	0.86	$51 838.27	0.84	$33 186.81	$859 774.58
	3	2	0.82	$58 399.63	0.78	$44 306.96	$324 814.26
	3	3	0.79	$65 551.06	0.72	$57 186.04	$128 533.79
	3	4	0.75	$73 375.89	0.66	$72 277.22	$12 661.35
	3.5	1	0.86	$51 450.95	0.84	$33 186.81	$764 935.04
	3.5	2	0.83	$57 559.20	0.78	$44 306.96	$277 513.82
	3.5	3	0.79	$54 178.60	0.72	$57 186.04	$97 620.34
	3.5	4	0.76	$71 376.12	0.66	$72 277.22	−$9 434.95
	4	1	0.86	$51 065.58	0.84	$33 186.81	$686 061.94
	4	2	0.83	$56 727.60	0.78	$44 306.96	$238 308.48
	4	3	0.80	$62 828.62	0.72	$57 186.04	$72 174.26
	4	4	0.77	$69 421.78	0.66	$72 277.22	−$27 392.93

ARR, absolute risk reduction; EDAS, encephaloduroarteriosynangiosis; ERSIAS-PC, encephaloduroarteriosynangiosis revascularization for symptomatic intracranial atherosclerotic steno-occlusive performance criterion; ICER, incremental cost-effectiveness ratio; IMM, intense medical management; QALY, quality-adjusted life-year.

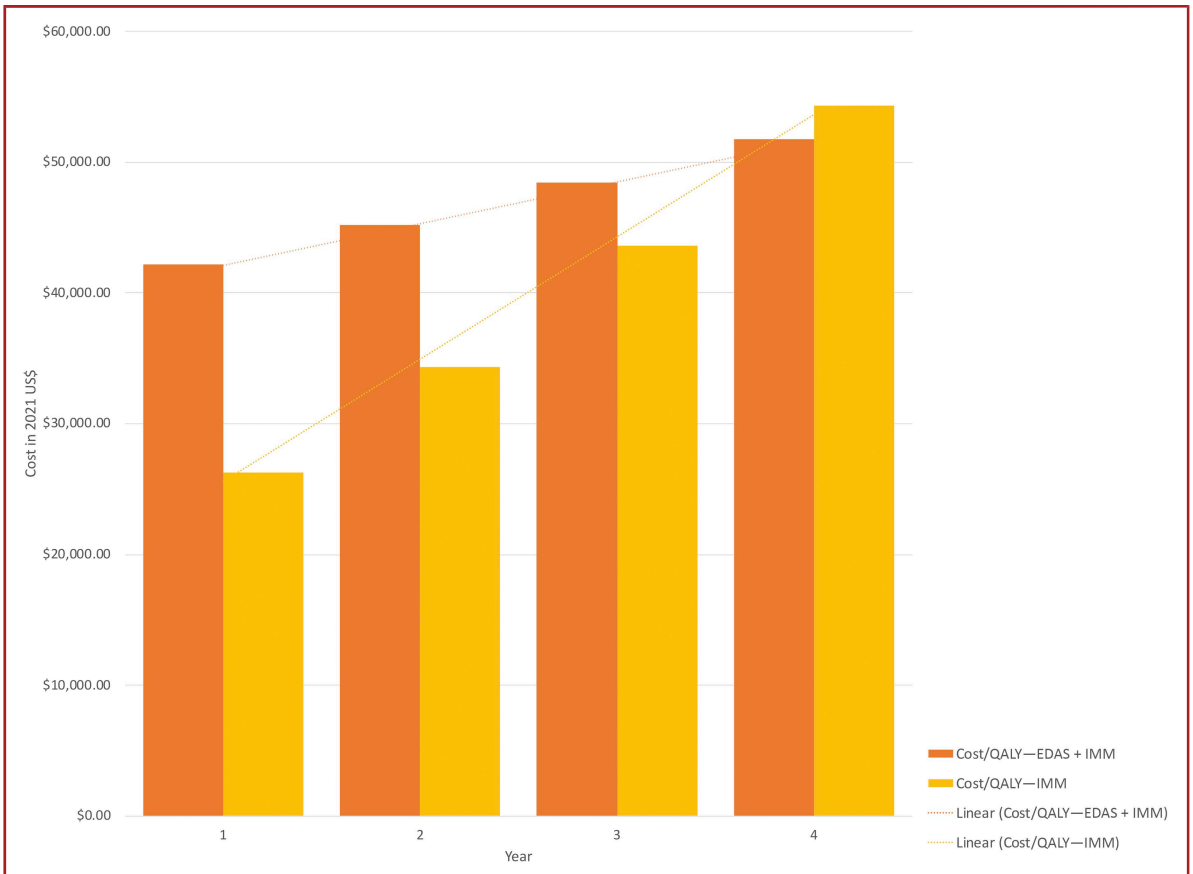

FIGURE 1. *Bar graphs depicting the calculated cost/QALY in ERSIAS-PC. ERSIAS-PC, encephaloduroarteriosynangiosis revascularization for symptomatic intracranial atherosclerotic steno-occlusive performance criterion; QALY, quality-adjusted life-year.*

stroke, and death were 3.5%, 0.95%, and 0.95% in the EDAS + IMM group and 9%, 5.9%, and 1.6% in the IMM group, respectively.[2]

The corresponding QALY, cost/QALY, and ICER for the ERSIAS-PC trial are summarized in Table 2 and Figures 1 and 2.

As expected with surgical treatments that have higher up-front risk and initial higher rates of events than medical management, the ICER was $474 451.37 during the first year, $162 441.61 for the second year, and $47 992.76 for the third year. The defined threshold for effectiveness was met between years 2 and 3.

For the second analysis, a more conservative range of ARR/year (2%-4 %) was projected to account for the anticipated reduction in effect size in a multicenter application of the technique. Once again, as expected, surgical treatment has higher up-front costs, as shown in Table 2. However, an ARR/year between 3.0% and 3.5%/year (50%-60% of the observed effect) demonstrated to be cost-effective after 2 to 3 years from the intervention (Figure 3).

DISCUSSION

In the evaluation of surgical interventions for the management of complex medical problems, considerations of CE are important to determine the benefit patients and communities may obtain from an intervention.[19] Surgeries usually incur in higher initial costs and perioperative risk than medical management. However, the additive long-term costs of treatment for conditions with high recurrent rates of stroke and disability such as ICAD should also be considered if an intervention can effectively reduce poor outcomes. The ERSIAS pilot study,[1] the ERSIAS-PC trial,[2,3] and the intermediate development trial of Zhang et al[4] have shown promising results using EDAS in patients with ICAD. Our analysis shows that in the population of the ERSIAS-PC trial, CE was reached at 2.5 years after surgery. Despite the initial higher costs, because of the operative and perioperative care, the gap between the costs narrows over time because the rates of stroke/death are lower for those who undergo EDAS + IMM.

As anticipated in the generalization of a technique to more centers, expected ARR/year should be more conservative than the

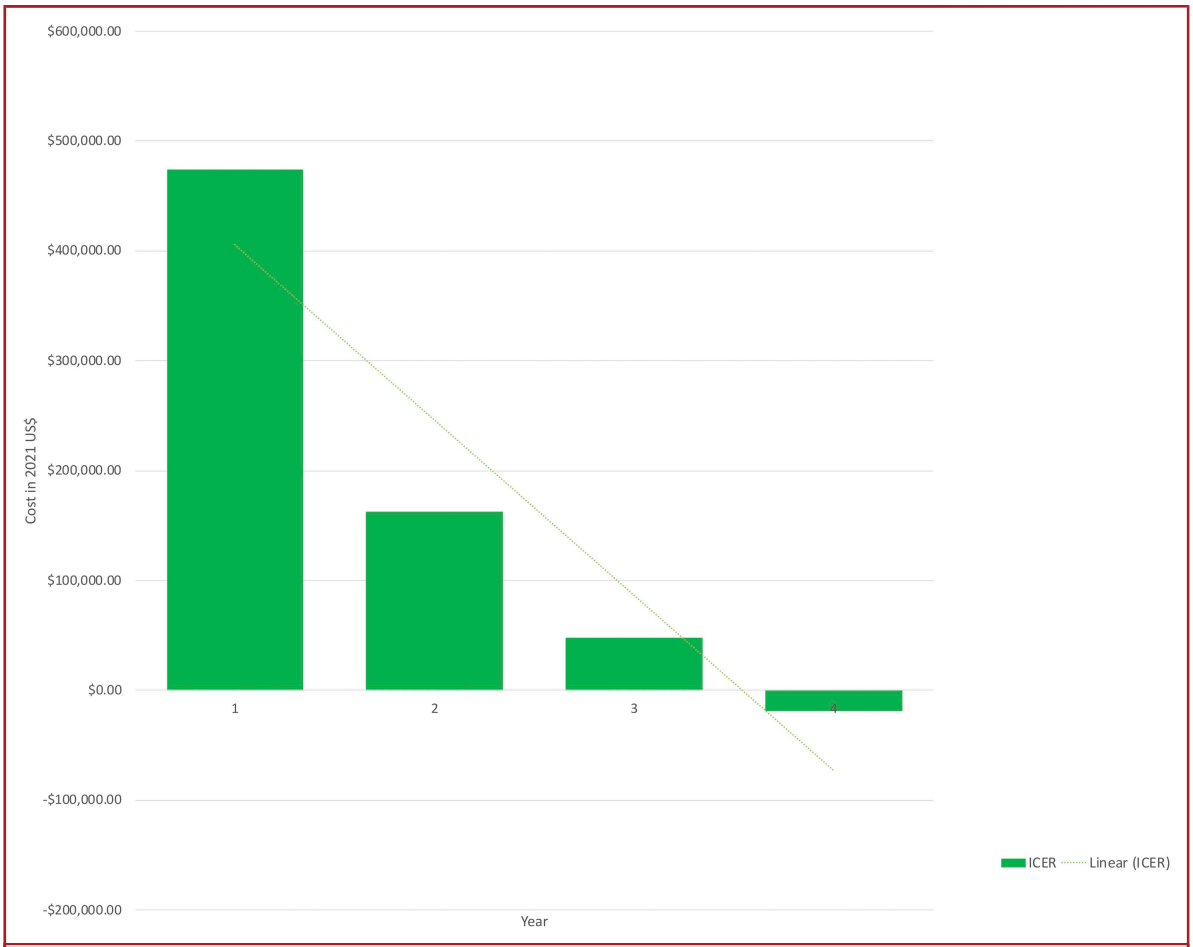

FIGURE 2. *Bar graphs depicting the calculated ICER in ERSIAS-PC. ERSIAS-PC, encephaloduroarteriosynangiosis revascularization for symptomatic intracranial atherosclerotic steno-occlusive performance criterion; ICER, incremental cost-effectiveness ratio.*

initially observed during earlier and intermediate development phases. For this reason, the more conservative projections of ARR of 2% to 4%/year, corresponding to 35% to 70% of the observed rates, were used in this projection. The analysis we present here demonstrates that the ARR of 3.0% to 3.5%/year, which corresponds to approximately 55% of the observed ERSIAS-PC ARR/year, is sufficient to reach CE of EDAS + IMM over IMM alone at 2 to 3 years.

The EDAS surgery is worth exploring in a phase III clinical trial given the positive results of the ERSIAS-PC trial, the growing interest in using this procedure to treat patients with high-risk ICAD, and the projections of its CE.

Limitations

This study is limited by the data obtained from the phase II ERSIAS-PC trial, which was an intermediate development study, powered not to demonstrate clinical effectiveness of the technique but to support the future development of a phase III trial. The use of linear models for ARR calculation was selected because it provided conservative estimate events, favoring the IMM group over the EDAS + IMM group; however, estimates based on probabilistic models cause unavoidable parameters uncertainty that needs to be confirmed in randomized clinical trials. Data presented here for estimations of potential future applications show that even with conservative ARR/year (55% of the observed effects in the phase II study), the procedure will still be cost-effective.

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Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

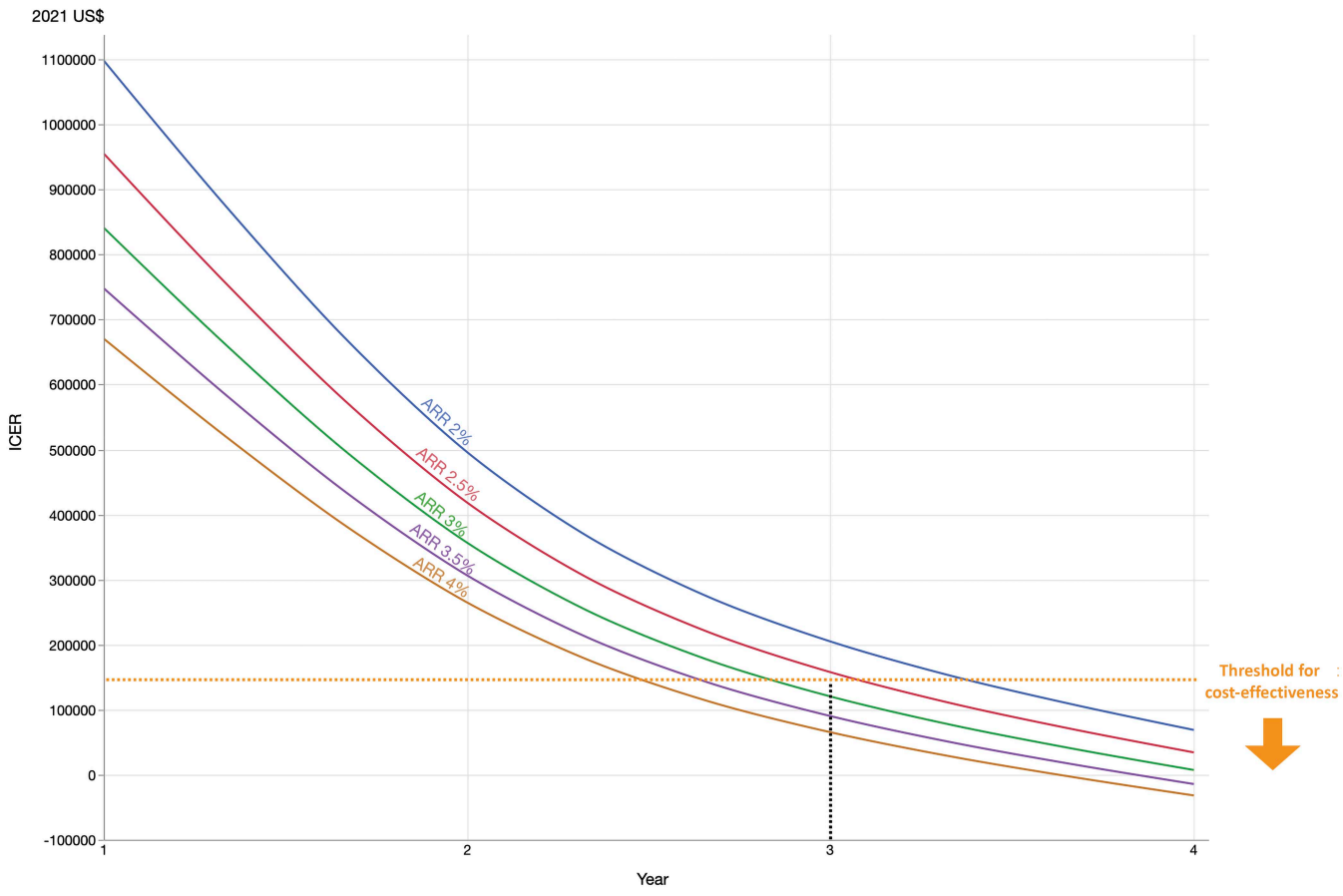

FIGURE 3. *Linear graph depicting the projected ICER over time after EDAS + IMM for different conservative projected ARR/year when compared with IMM alone. An ARR/year between 3.0% and 3.5% crosses the CE threshold after 2 to 3 years from the intervention. ARR, absolute risk reduction; CE, cost-effectiveness; EDAS, encephaloduroarteriosynangiosis; IMM, intense medical management.*

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