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Utility-Weighted Decision Analysis of Endovascular Therapy for Medium-Vessel-Occlusion Stroke Using Full Modified Rankin Scale Distributions From Three Randomized Trials

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Abstract

Purpose.

Randomized trials of endovascular therapy (EVT) for stroke due to medium-vessel occlusion (MeVO) are discordant and did not share a common dichotomous primary endpoint. We reconciled them by converting each arm's full 7-level modified Rankin Scale (mRS) distribution into expected utility.

Methods.

We performed a trial-specific, non-pooled utility-weighted decision analysis of ORIENTAL-MeVO, DISTAL, and ESCAPE-MeVO. Arm-level mRS counts were derived deterministically from the published intention-to-treat distributions and verified against reported anchor counts. The utility-weighted mRS difference (EVT minus control) was estimated by Dirichlet probabilistic sensitivity analysis with common random numbers across utility mappings. Symptomatic intracranial hemorrhage (sICH) and mortality were parallel safety outcomes.

Results.

The direction of the point estimate differed across trials. In ORIENTAL-MeVO the utility-weighted mRS difference was positive (+ 0.054; 95% credible interval [CrI] − 0.007 to + 0.115; probability of positive net benefit 0.96), whereas in DISTAL (− 0.014; 95% CrI − 0.071 to + 0.042; probability 0.31) and ESCAPE-MeVO (− 0.034; 95% CrI − 0.092 to + 0.024; probability 0.13) the point estimates were negative. All three credible intervals crossed zero. Direction was stable across utility mappings and aligned with baseline severity and thrombolysis exposure. sICH was more frequent with EVT.

Conclusion.

The net functional benefit of MeVO EVT is not uniform; the most favorable point estimate occurred in the higher-severity, lower-thrombolysis trial population. A favorable dichotomous result may overstate benefit once the full disability distribution and safety are considered, supporting severity- and selection-based decision-making.

Introduction

Endovascular thrombectomy is a highly effective treatment for acute ischemic stroke caused by large-vessel occlusion [1]. Whether this benefit extends to medium-vessel occlusion (MeVO) has been uncertain: the downstream ischemic territory is smaller and spontaneous or thrombolysis-related recanalization is more frequent, so the balance between procedural benefit and procedural harm is less favorable a priori [2].

Recent randomized trials have produced discordant results. ORIENTAL-MeVO reported a significant improvement in functional independence with endovascular therapy (EVT) [3], whereas DISTAL and ESCAPE-MeVO did not demonstrate a favorable primary result and raised concerns about the balance between functional benefit and procedural harm, including higher symptomatic intracranial hemorrhage (sICH) and, in ESCAPE-MeVO, higher mortality [4, 5]. These trials differ materially in baseline stroke severity, intravenous thrombolysis (IVT) exposure, geography, and design, and they did not use a common dichotomous primary endpoint: functional independence (modified Rankin Scale [mRS] 0–2) in ORIENTAL-MeVO and DISTAL, but an excellent outcome (mRS 0–1) in ESCAPE-MeVO after the proportional-odds assumption was not met.

Dichotomized endpoints discard information about the direction and magnitude of ordinal disability shifts and do not weight health states by patient value; a difference concentrated at one dichotomy threshold can therefore look favorable while the overall value-weighted shift is neutral or unfavorable, particularly when a procedure also increases the risk of severe outcomes. Utility-weighting of the full mRS distribution addresses both problems and places trials with different dichotomous endpoints on a common scale [6–9].

We therefore reconciled the discordant MeVO EVT trials with a trial-specific, utility-weighted decision analysis of their full mRS distributions. Our aim was to determine whether the net functional benefit of EVT differs across these trials, whether any such difference is robust to the choice of utility mapping and to safety, and how it relates to patient selection — the severity and thrombolysis profile of the enrolled populations.

Materials and Methods

Design and Data Sources

This is a trial-specific, utility-weighted decision analysis of EVT versus best medical treatment or usual care for MeVO stroke, using the full 7-level mRS distribution of each arm. It is a secondary analysis of published aggregate trial data; it involves no individual patient data and is not a cost-effectiveness analysis, because no cost inputs are used and results are expressed in health terms only.

The core analysis includes the three trials that report a complete, peer-reviewed, arm-level ordinal mRS distribution: ORIENTAL-MeVO [3], DISTAL [4], and ESCAPE-MeVO [5]. Trials without complete peer-reviewed arm-level ordinal mRS distributions suitable for reproducible utility-weighted analysis, including DISCOUNT and DISTALS, were excluded from the core analysis and may be added as clearly labeled sensitivity scenarios when complete data become available. Trials were analyzed separately and not pooled, because the enrolled populations differ materially in baseline stroke severity, IVT exposure, geography, and design, and because the trials did not share a common dichotomous endpoint.

Derivation of the Ordinal Input Distributions

The three trials report their intention-to-treat (ITT) ordinal distributions in different formats, so arm-level mRS category counts were obtained by a trial-specific deterministic derivation and verified against anchor counts reported separately in each trial. In ORIENTAL-MeVO, the category counts were obtained by differencing the cumulative counts reported for mRS 0, 0–1, 0–2, 0–3, 0–4, and 0–5 [3]. In ESCAPE-MeVO, the ITT category percentages reported to one decimal place with their arm denominators admit exactly one compatible integer count per category, so the recovery is unique [5]. In DISTAL, the ITT distribution reports mRS 0 through 4 and a combined “5 or 6” category; category counts were recovered in the same way, and the 5-versus-6 split was obtained from the separately reported 90-day death counts, which is exact because all deaths lie within the mRS-analyzed set (in the control arm the three participants without an mRS score withdrew consent while alive) [4]. The inversion used for ESCAPE-MeVO and DISTAL presumes that each published percentage equals the category count divided by the stated arm denominator, rounded to one decimal place; ORIENTAL-MeVO requires no such presumption. Each derivation reproduced the anchor counts reported by its trial — mRS 6 versus reported deaths in ORIENTAL-MeVO; mRS 0–1, mRS 0–2, and deaths in ESCAPE-MeVO; mRS 0–1 in DISTAL — and all arms summed to their denominators. Denominator conventions follow the source trials: the DISTAL ordinal distribution uses the mRS-analyzed control denominator (269) whereas its mortality risk difference uses the randomized denominator (272), and ESCAPE-MeVO sICH is reported in the as-treated safety population.

Model and Utility Mapping

For each trial and arm, expected utility was computed as the sum over mRS levels of the category probability multiplied by its utility weight, and the trial-specific outcome was the utility-weighted mRS difference (UW-mRS difference; EVT expected utility minus control expected utility). Death was incorporated through the mRS 6 category.

The base-case utility weights were the acute ischemic stroke values of Wang et al., taken at full reported precision from the acute ischemic stroke column of their Data Supplement Table III (mRS 0–6: 0.96633, 0.88979, 0.73767, 0.56522, 0.27721, − 0.08642, 0) [6]. Pre-specified sensitivity analyses repeated the analysis with the all-stroke values from the same table [6], the Rivero-Arias EQ-5D mapping [7], the Chaisinanunkul utility-weighted mRS values [8], a robustness analysis truncating the negative mRS 5 utility to zero, and the rounded vector printed in the abstract of Wang et al., which corresponds to neither column of that table and was therefore retained only as a discrepancy test [6].

To confirm that the derived counts could not drive the findings, we performed an adversarial analysis in which one patient per arm was moved between mRS categories in the direction most damaging to each trial's observed result, and the analysis was re-run.

Uncertainty, Sensitivity, and Safety

Arm-level mRS probabilities were modeled with a Dirichlet distribution (Jeffreys prior; 20,000 iterations; fixed seed). Common random numbers were used across utility-mapping sensitivity analyses, so that differences between sensitivity results reflect the utility mapping rather than Monte Carlo noise. For each trial we report the mean UW-mRS difference with a 95% credible interval (CrI) and the probability that EVT provides a positive net benefit.

sICH and mortality were analyzed as parallel safety outcomes and were not added as separate utility penalties, to avoid double counting, because death is already represented through the mRS 6 category; the authoritative safety inference for each trial is that trial's own adjusted estimate.

Threshold Extension

To indicate the longer-horizon implication of the 90-day result without a full lifetime model, we projected the 90-day UW-mRS difference over post-90-day 1-year and 5-year extension horizons (assuming the 90-day utility difference persists for 1 or 5 additional years) under durable-retention scenarios (ρ, the fraction of the 90-day utility difference retained in each additional year; ρ = 1.00, 0.75, 0.50, 0.25) with a 3% annual discount rate. For trials with a positive 90-day difference, we estimated the maximum tolerable additional post-90-day quality-adjusted life-year (QALY)-equivalent loss at which EVT would remain at break-even — a combined delayed-harm budget, not an estimate of excess mortality risk. For trials with a negative 90-day difference, we estimated the additional durable utility benefit required to offset the early disadvantage. Lifetime projection and value-of-information analysis were deferred to an exploratory supplement.

Reproducibility

The analysis code, the verified parameter table, the input distributions with their derivation provenance, the count-derivation verification script, and the random seed will be deposited in a public repository; an anonymized copy is available to the editors and reviewers on request. This is a transparency-oriented secondary analysis of public data, not a prospective preregistration. A large language model was used to assist with language editing and general manuscript review. The study design, derivation and verification of all inputs, analysis code, interpretation of results, and final text were performed and checked by the authors, who take full responsibility for the content.

Results

Primary Analysis

The direction of the point estimate differed across trials (Table 1; Fig. 1a). In ORIENTAL-MeVO, the UW-mRS difference was positive (mean + 0.054; 95% CrI − 0.007 to + 0.115), with a high posterior probability of positive net benefit (0.96). In DISTAL and ESCAPE-MeVO, the point estimates were negative (means − 0.014 and − 0.034), with low probabilities of positive net benefit (0.31 and 0.13; equivalently, posterior

probabilities that control is superior of 0.69 and 0.87). All three credible intervals crossed zero, so no trial provides a value-weighted advantage that is definitive at the 95% level; the trials nevertheless differ in the direction of the estimate and in the posterior probability of net benefit. In particular, the ORIENTAL-MeVO interval grazed zero despite the high probability of net benefit, indicating a positive but not definitive value-weighted advantage once the full disability distribution was considered.

Table 1
Trial-specific utility-weighted net benefit and safety

Trial	Median NIHSS	IVT (%)	UW-mRS difference (95% CrI)	P(net benefit > 0)	sICH risk difference (pp)	Mortality, EVT vs control
ORIENTAL-MeVO	10	36.6	+ 0.054 (− 0.007, + 0.115)	0.96	+ 2.5	11.1% vs 10.2%
DISTAL	6	65.4	−0.014 (− 0.071, + 0.042)	0.31	+ 3.3	11.8% vs 10.7%
ESCAPE-MeVO	8	58.4[a]	−0.034 (− 0.092, + 0.024)	0.13	+ 3.2	13.3% vs 8.4%[b]

Estimates are means of 20,000 Dirichlet draws with a Jeffreys prior and a fixed seed. The base-case utility mapping is the acute ischemic stroke column of the Wang et al. Data Supplement Table III, used at full reported precision [6].

CrI credible interval, EVT endovascular therapy, IVT intravenous thrombolysis, NIHSS National Institutes of Health Stroke Scale, pp percentage points, sICH symptomatic intracranial hemorrhage, UW-mRS utility-weighted modified Rankin Scale

a IVT exposure is trial-level (both arms pooled); this value is derived from the arm-level counts reported in that trial, because a trial-level value is not reported.

b Trial-reported adjusted hazard ratio 1.82 (95% confidence interval 1.06–3.12).

Relationship to Patient Selection

The direction of net benefit tracked the severity and thrombolysis profile of the trial populations. ORIENTAL-MeVO enrolled a more severely affected, lower-IVT population (median baseline National Institutes of Health Stroke Scale [NIHSS] score 10; IVT 36.6%), whereas DISTAL and ESCAPE-MeVO enrolled less severely affected, higher-IVT populations (median NIHSS 6 and 8; IVT 65.4% and 58.4%). This cross-trial relationship is shown in Fig. 1b; it is descriptive and is not a formal trial-level meta-regression, which would be underpowered and subject to ecological bias with three trials.

Sensitivity to Utility Mapping

The trial-specific conclusions were stable across all alternative utility mappings (Wang all-stroke, Rivero-Arias, Chaisinanunkul, and mRS 5 truncation) and across the discrepant Wang abstract vector: the UW-mRS difference remained positive for ORIENTAL-MeVO (means + 0.047 to + 0.054; probability of net benefit 0.94–0.96) and negative for DISTAL (− 0.017 to − 0.014; probability 0.27–0.31) and ESCAPE-MeVO (− 0.035 to − 0.030; probability 0.12–0.15). The direction of net benefit was therefore not an artifact of the utility mapping.

Robustness of the Derived Distributions

The direction of net benefit in every trial survived an adversarial single-patient misallocation in both arms simultaneously (ORIENTAL-MeVO + 0.047; DISTAL − 0.007; ESCAPE-MeVO − 0.026). A simultaneous one-patient adversarial move in both arms can change the arm-pair contrast by at most (u_max − u_min) (1/N_EVT + 1/N_control), which was 0.008 or less across trials and smaller than every observed absolute difference. The trial-specific directions therefore cannot be an artifact of the count derivation.

Safety

sICH was more frequent with EVT across the three trials (crude risk differences + 2.5, + 3.3, and + 3.2 percentage points in ORIENTAL-MeVO, DISTAL, and ESCAPE-MeVO). Mortality was numerically higher with EVT in each trial and, in ESCAPE-MeVO, significantly higher on that trial's own adjusted analysis (adjusted hazard ratio 1.82; 95% confidence interval 1.06–3.12); the DISTAL and ORIENTAL-MeVO mortality differences were small and not significant. Because death is already represented in the utility model through mRS 6, these safety outcomes are reported as parallel measures rather than additional penalties.

Threshold Extension

Over a post-90-day 5-year extension horizon at full persistence (ρ = 1.00), the projected discounted difference was + 0.245 QALY-equivalent in ORIENTAL-MeVO (95% CrI − 0.033 to + 0.525) — the value-weighted margin available to absorb additional post-90-day harm before break-even (Table 2). In DISTAL and ESCAPE-MeVO the projected differences were − 0.066 (95% CrI − 0.324 to + 0.192) and − 0.154 (95% CrI − 0.419 to + 0.109), whose absolute values are the additional durable benefit that would be required to reach break-even; all three intervals crossed zero. Because the projection is a positive scalar multiple of the 90-day difference, the sign and the probability of net benefit are invariant to the retention scenario and the horizon.

Table 2
Bounded threshold extension (base-case utility mapping, 3% annual discount)

Trial	90-day direction	Projected difference, post-90-day 1 year (rho = 1.00)	Projected difference, post-90-day 5 years (rho = 1.00), mean (95% CrI)	Interpretation
ORIENTAL-MeVO	Positive	+ 0.052	+ 0.245 (− 0.033, + 0.525)	Value-weighted margin of 0.245 QALY-equivalent available before break-even (delayed-harm budget)
DISTAL	Negative	−0.014	−0.066 (− 0.324, + 0.192)	0.066 QALY-equivalent additional durable benefit required to break even
ESCAPE-MeVO	Negative	−0.033	−0.154 (− 0.419, + 0.109)	0.154 QALY-equivalent additional durable benefit required to break even

Projected discounted QALY-equivalent difference = rho × (90-day UW-mRS difference) × annuity(H, 3%), where rho is the assumed fraction of the 90-day utility difference retained in each additional year and H is the post-90-day horizon.

All values are reported on the signed projected-difference scale (endovascular therapy minus control). For trials with a negative projected difference, the absolute value of that difference is the additional durable benefit that would be required to reach break-even; the credible interval is reported on the same signed scale and crosses zero, indicating that the projected difference remains compatible with both benefit and harm.

Because the projection is a positive scalar multiple of the 90-day difference, the sign and the probability of net benefit are invariant to rho and to the horizon. The delayed-harm budget is a combined value-weighted margin and is not an estimate of excess mortality.

CrI credible interval, QALY quality-adjusted life-year, UW-mRS utility-weighted modified Rankin Scale

Discussion

In a trial-specific utility-weighted decision analysis of three randomized trials, the net functional benefit of EVT for MeVO was not uniform. The most favorable point estimate occurred in ORIENTAL-MeVO — the trial that enrolled a more severely affected, lower-thrombolysis population — whereas DISTAL and ESCAPE-MeVO had neutral-to-unfavorable point estimates; all uncertainty intervals crossed zero. Two aspects of this reading matter. First, a favorable dichotomous result may overstate the magnitude or certainty of benefit once the full ordinal disability shift and procedural safety are considered; even the positive ORIENTAL-MeVO point estimate had a value-weighted credible interval that grazed zero. Second,

the direction of the trial-specific point estimates was stable across utility mappings, so the divergence across trials reflects differences between the trials rather than the choice of utility values.

The threshold extension provides a simple, scenario-based translation of the 90-day UW-mRS difference to a longer horizon, without estimating an observed long-term QALY gain. Under a durable-benefit assumption, the ORIENTAL-MeVO point estimate corresponded to a modest QALY-equivalent budget to absorb later harm, whereas DISTAL and ESCAPE-MeVO would each require additional durable benefit — not observed in the trials — for EVT to become value-neutral.

Taken together, the three trials are more consistent when viewed through differences in baseline severity, thrombolysis exposure, and procedural risk. This aggregate analysis cannot establish patient-level effect modification, but it provides a trial-level, patient-centered framework for interpreting discordant MeVO EVT results. The trials that did not show benefit enrolled less severely affected patients with high thrombolysis exposure, in whom the control arm already achieves good outcomes and the incremental value of a procedure that also increases hemorrhage risk is small; the trial with the positive point estimate enrolled more severely affected, lower-thrombolysis patients, in whom the reperfusion opportunity is larger. For neuroradiology and neurointerventional practice, these findings suggest that MeVO EVT should be interpreted through an imaging- and severity-based selection framework — anchored on baseline deficit, occlusion characteristics on baseline imaging, and thrombolysis candidacy — rather than through a uniform vessel-category indication.

Limitations

The analysis has important limitations. The source trials report the ordinal distribution as cumulative counts (ORIENTAL-MeVO) or as category percentages with denominators (DISTAL, ESCAPE-MeVO) rather than as directly tabulated category counts; the category counts used here were therefore derived deterministically from those reported quantities and verified against independently reported anchor counts, rather than transcribed from a published category-count table. The trial supplements do not tabulate the ITT ordinal distributions, reporting only per-protocol or as-treated distributions. The direction of net benefit was nevertheless unchanged under an adversarial single-patient misallocation in both arms of every trial. Only three trials constitute the core, so between-trial variance is not reliably estimable and trials were analyzed separately rather than pooled; DISCOUNT and DISTALS were not included in the core analysis because complete peer-reviewed arm-level ordinal mRS distributions suitable for reproducible utility-weighted analysis were not available at the time of analysis. The utility mappings are external rather than trial-collected, although the direction of net benefit was robust across several verified mappings. The association of net benefit with severity and thrombolysis is trial-level and interpretive, not individual-level effect modification. Finally, no costs were used; this is a decision analysis in health terms and not an economic evaluation.

Conclusion

The net functional benefit of endovascular therapy for MeVO stroke is not uniform across randomized trials. When the full mRS distribution is weighted by patient value and procedural safety is considered, only the higher-severity, lower-thrombolysis trial population showed a positive point estimate, and a favorable dichotomous endpoint may overstate the magnitude or certainty of benefit. These findings support severity- and selection-based decision-making in MeVO thrombectomy.

Declarations

Ethical standards. The manuscript does not contain clinical studies or patient data. This work is a secondary analysis of aggregate results already published in the cited randomized trials; no individual participant data were accessed, and institutional review board approval and informed consent were therefore not applicable.

Conflict of interest.

The authors declare that they have no conflict of interest.

Author Contribution

H.D.Y. and S.Y.C. conceived the study. H.D.Y. designed the analytic framework, derived the input distributions, performed the statistical analysis, prepared the analysis code, figures, and tables, and drafted the manuscript. H.D.Y. and J.G.K. verified the extracted trial data and input distributions. J.G.K. critically reviewed the clinical interpretation and edited the manuscript. S.Y.C. supervised the study and critically reviewed and edited the manuscript. All authors reviewed and approved the final manuscript.

Data and code availability.

All data analyzed in this study are contained in the published reports of the cited randomized trials. The analysis code, parameter table, derived input distributions, and verification script will be deposited in a public repository; an anonymized copy is available to the editors and reviewers on request.

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Figures

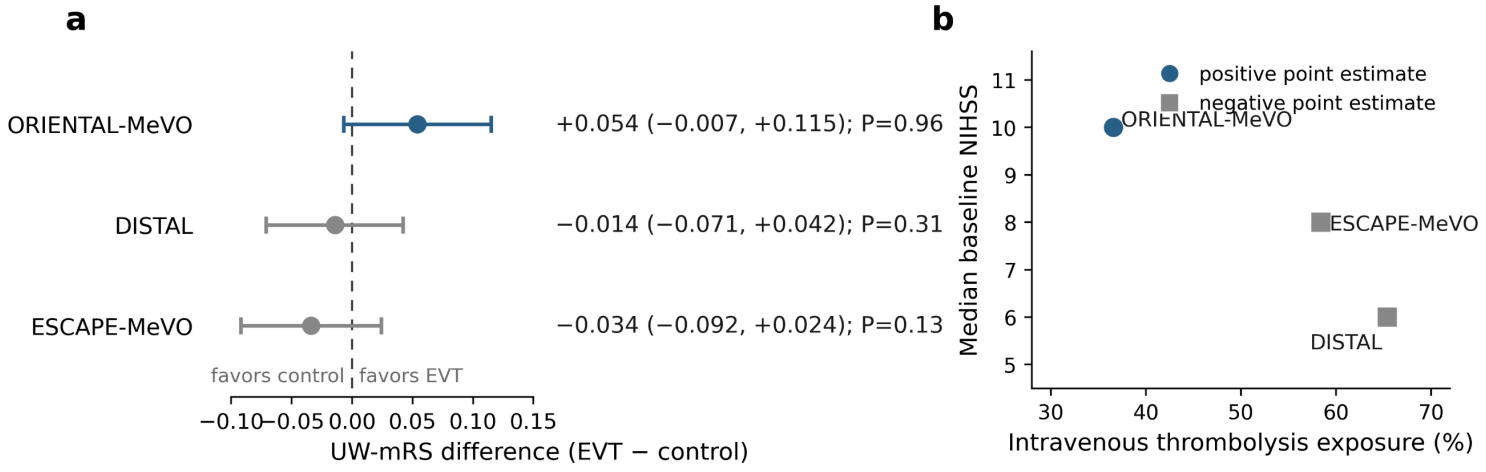


Figure 1

Trial-specific utility-weighted net benefit and trial-selection context. **a** 90-day utility-weighted modified Rankin Scale (UW-mRS) difference for each trial, defined as expected utility in the endovascular therapy (EVT) arm minus expected utility in the control arm. Points indicate posterior means and horizontal bars indicate 95% credible intervals from Dirichlet probabilistic sensitivity analysis; the vertical dashed line

indicates no difference. Values to the right of each row give the posterior mean (95% credible interval) and the posterior probability that EVT confers a positive net benefit. **b** Trials positioned by median baseline National Institutes of Health Stroke Scale (NIHSS) score and intravenous thrombolysis exposure. ORIENTAL-MeVO enrolled the highest-severity, lowest-thrombolysis population and had a positive utility-weighted point estimate (circle), whereas DISTAL and ESCAPE-MeVO enrolled lower-severity, higher-thrombolysis populations and had negative point estimates (squares). This cross-trial pattern is descriptive and does not constitute a trial-level meta-regression