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Original Article

Cost-Effectiveness of Late Endovascular Thrombectomy vs. Best Medical Management in a Clinical Trial Setting and Real-World Setting

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ABSTRACT: *Background and purpose:* To assess cost-effectiveness of late time-window endovascular treatment (EVT) in a clinical trial
setting and a "real-world" setting. *Methods:* Data are from the randomized ESCAPE trial and a prospective cohort study (ESCAPE-LATE).
Anterior circulation large vessel occlusion patients presenting > 6 hours from last-known-well were included, whereby collateral status
was an inclusion criterion for ESCAPE but not ESCAPE-LATE. A Markov state transition model was built to estimate lifetime costs and
quality-adjusted life-years (QALYs) for EVT in addition to best medical care vs. best medical care only in a clinical trial setting (comparing
ESCAPE-EVT to ESCAPE control arm patients) and a "real-world" setting (comparing ESCAPE-LATE to ESCAPE control arm patients).
We performed an unadjusted analysis, using 90-day modified Rankin Scale(mRS) scores as model input and analysis adjusted for baseline
factors. Acceptability of EVT was calculated using upper/lower willingness-to-pay thresholds of 100,000 USD/50,000 USD/QALY. *Results:*
Two-hundred and forty-nine patients were included (ESCAPE-LATE:*n* = 200, ESCAPE EVT-arm:*n* = 29, ESCAPE control-arm:*n* = 20). Late
EVT in addition to best medical care was cost effective in the unadjusted analysis both in the clinical trial and real-world setting, with
acceptability 96.6%–99.0%. After adjusting for differences in baseline variables between the groups, late EVT was marginally cost effective in
the clinical trial setting (acceptability:49.9%–61.6%), but not the "real-world" setting (acceptability:32.9%–42.6%). *Conclusion:* EVT for
LVO-patients presenting beyond 6 hours was cost effective in the clinical trial setting and "real-world" setting, although this was largely related
to baseline patient differences favoring the "real-world" EVT group. After adjusting for these, EVT benefit was reduced in the trial setting, and
absent in the real-world setting.

RÉSUMÉ : **Analyse coût-efficacité de la thrombectomie endovasculaire tardive par rapport à la meilleure prise en charge médicale dans le
cadre d'un essai clinique randomisé et dans un contexte réel** *Contexte et objectif :* Analyser le rapport coût-efficacité de la thrombectomie
endovasculaire (TEV) tardive dans le cadre d'un essai clinique randomisé et dans un contexte réel. *Méthodes :* Les données obtenues
proviennent d'un essai clinique randomisé de type ESCAPE (*Endovascular treatment for Small Core and Anterior circulation Proximal
occlusion with Emphasis on minimizing CT to recanalization times*) et d'une étude de cohorte prospective de type ESCAPE-LATE. Les patients
souffrant d'une occlusion de gros vaisseaux de la circulation antérieure et s'étant présentés aux urgences plus de 6 heures après la dernière fois
où l'on avait observé une absence de signes et de symptômes de l'AVC actuel ont été inclus dans cette étude, l'état de la circulation collatérale
étant un critère d'inclusion pour un essai clinique randomisé de type ESCAPE mais pas pour une étude de type ESCAPE-LATE. Un modèle de
transition d'état de Markov a été par ailleurs élaboré pour estimer les coûts à vie et les années de vie ajustées en fonction de la qualité de vie
(indicateur QALY) pour la TEV et pour déterminer les meilleurs soins médicaux en comparaison avec les meilleurs soins médicaux prodigués
uniquement dans le cadre d'un essai clinique randomisé (comparant les résultats de l'essai de type ESCAPE à ceux de patients d'un groupe
témoin ESCAPE) et dans un contexte réel (comparant les résultats d'une étude de cohorte de type ESCAPE-LATE à ceux de patients d'un

groupe témoin ESCAPE). Comme données d'entrée du modèle, nous avons aussi effectué une analyse non ajustée en utilisant les scores de l'échelle de Rankin modifiée (ERm) au bout de 90 jours ainsi qu'une analyse ajustée pour les facteurs de base. L'acceptabilité de la TEV a été calculée en utilisant les seuils supérieurs et inférieurs (100 000 $ et 50 000 $ américains/QALY) de la volonté de payer. ***Résultats :*** Au total, 249 patients ont été inclus (étude de cohorte ESCAPE-LATE : *n* = 200 ; essai clinique randomisé de type ESCAPE (témoins) : *n* = 29 ; essai de type ESCAPE (témoins) : *n* = 20). En plus des meilleurs soins médicaux, la TEV tardive s'est avérée rentable dans l'analyse non ajustée, et ce, tant en ce qui concerne l'essai clinique randomisé que dans un contexte réel, avec une acceptabilité de 96,6 % à 99,0 %. Après ajustement des différences de variables de base entre les groupes, la TEV tardive s'est révélée marginalement rentable dans le cadre de l'essai clinique randomisé (acceptabilité : 49,9 % - 61,6 %), mais pas dans un contexte réel (acceptabilité : 32,9 % - 42,6 %). ***Conclusion :*** La TEV pour les patients souffrant d'une occlusion des gros vaisseaux se présentant aux urgences pour des soins, et ce, après 6 heures était rentable dans le cadre d'un essai clinique randomisé et dans un contexte réel bien que cela puisse être largement attribuable aux différences initiales entre les patients, ce qui favorise le groupe de patients de l'essai clinique randomisé par rapport au contexte réel. Après ajustement de ces différences, le bénéfice de la TEV s'est révélé réduit dans le cadre de l'essai clinique randomisé et absent dans un contexte réel.

Introduction

Endovascular thrombectomy (EVT) has been shown to be safe and efficacious in acute ischemic stroke patients with large vessel occlusion (LVO) presenting between 6 and 24 hours from last known well in several randomized controlled trials.[1–3] The results of these trials showed a large EVT treatment benefit and were used as a basis to prove the cost-effectiveness of late-time window EVT.[4–6] However, these results may not necessarily be applicable to "real world", because of the strict trial eligibility criteria which may have led to patient over-selection, a higher degree of treatment and workflow standardization in a trial setting vs. clinical routine, and because physicians may – consciously or subconsciously – treat patients who are enrolled in clinical trials differently from non-trial patients. One study has assessed cost-effectiveness of late time-window EVT using "real-world" data(ie, non-trial data) in the Australian healthcare setting.[7] However, the health economic impact of late time window EVT in a randomized trial setting has not been directly compared to the "real-world" setting yet. Thus, it is unclear whether trial-derived cost-effectiveness metrics for late time window EVT also apply to patients treated in clinical routine.[4–6]

We used pooled data of late time-window patients from the randomized controlled ESCAPE trial(8) and ESCAPE-LATE, a prospective multicenter cohort study of EVT patients treated beyond 6 hours from last-known-well in former ESCAPE sites, to assess and compare cost-effectiveness of late time-window EVT in a clinical trial setting and in clinical routine ("real-world setting").

Methods

Patient sample

We pooled patient level data from the randomized controlled ESCAPE trial and a multicenter prospective cohort study (ESCAPE-LATE), which was conducted in former ESCAPE trial sites after completion of the ESCAPE trial (Suppl. Figure 1).

ESCAPE trial

The randomized controlled ESCAPE trial[8] randomized patients who presented up to 12 hours from last know well 1:1 to EVT in addition to best medical care vs. best medical care only. The trial design had relatively pragmatic inclusion criteria compared to other EVT trials: adult patients were eligible for the trial if they had an occlusion of the intracranial internal carotid artery, M1 or proximal M2 segment of the middle cerebral artery, presented within 12 hours of symptom onset, had a pre-stroke Barthel Index ≥ 90, a baseline Alberta Stroke Program Early CT Score (ASPECTS) ≥ 6 and moderate to good collaterals on CTA. The primary outcome was functional outcome, as measured by the 90-day modified Rankin Score (mRS). The ethics board at each participating site approved the trial, and consent was obtained from the patient or a legal representative, or deferral of consent processes were used according to the local laws and regulations. Since we aimed to assess cost-effectiveness of late time window EVT, we only included trial patients who presented beyond 6 hours from last known well.

ESCAPE-LATE

ESCAPE-LATE was a multicenter, prospective cohort study that enrolled patients treated beyond 6 hours from last known well in clinical routine at 10 high-volume ESCAPE trial sites. The study enrolled patients from February 2015 (when the ESCAPE trial was stopped after an interim analysis) to December 2017 (when the DAWN and DEFUSE-3 trials were published). Adult patients were eligible if they underwent EVT with a time from last known well to groin puncture time > 6 hours. There were no imaging-specific enrolment criteria; in particular, no ASPECTS or ischemic core thresholds were applied and no advanced imaging was needed for enrolment. Those patients meeting the eligibility criteria and treated in clinical routine were identified by the site coordinators and their data was entered into an electronic case report form (RedCap). The primary outcome was a functional outcome, as measured by the 90-day mRS. Since all variables collected were captured as part of clinical routine care, the local ethics committee approved the study with waiver of consent. To ensure comparability with late time window ESCAPE patients, we only included ESCAPE-LATE patients with anterior circulation LVO (terminal internal carotid artery, M1 segment or M2 segment of the middle cerebral artery).

Model structure

We used TreeAge Pro 2022, version 2.0 (TreeAge Pro Software, Inc.) to build a decision model with 3 arms – one representing the ESCAPE trial EVT group, the ESCAPE trial control group and the ESCAPE LATE EVT group (Fig. 1a). The model consisted of two parts: an initial short-term model with a 3-month cycle that incorporated costs and outcomes within the first 3 months after the
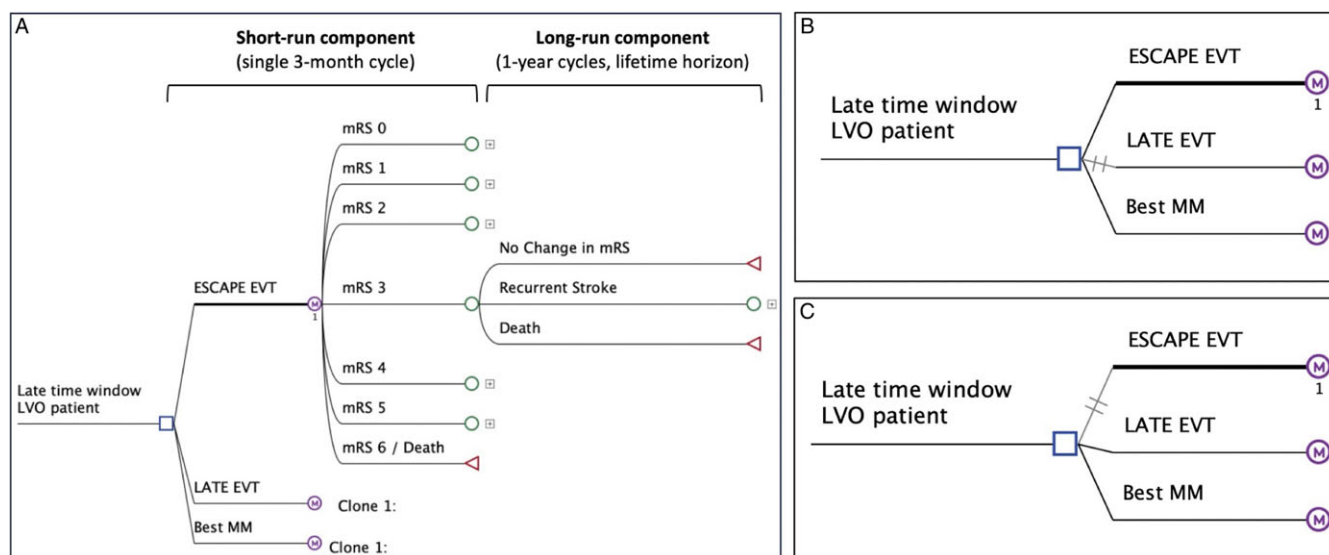
Figure 1. Cost-effectiveness model used in this analysis. (***a***) shows the overall model structure. The model had three arms, simulating lifetimes costs and quality-adjusted life years for each of the following three late-time window large vessel occlusion patient groups: (1) ESCAPE trial endovascular thrombectomy (EVT) group (upper arm in [A]), (2) ESCAPE LATE study EVT group (middle arm in [A]), and (3) ESCAPE trial best medical management arm (lower arm in [C]). The model consisted of an initial single 3-month cycle (short run component), in which patients were assigned one of 7 health states (mRS 06), followed by a long-run Markov state transition long-run component with a 12-month cycle length. In the long-run component, patients in the mRS 05 health states could either remain in the same health state, suffer a recurrent stroke and deteriorate to a worse health state or die, either due to recurrent stroke or age-related mortality. Purple round nodes indicate Markov (M) nodes, green round nodes indicate recursive nodes and red triangular nodes indicate terminal nodes. "Clone 1" indicates the same subtree structure in arms 2 and 3 (collapsed in the figure for better oversight). In the first analysis set, the ESCAPE trial EVT group was compared to the ESCAPE trial control group ("trial setting"), and the ESCAPE-LATE group was excluded from the analysis (shown by the two crossed lines in [B]). In the second analysis set, the ESCAPE LATE EVT group was compared to the ESCAPE trial control group ("real-world setting"), and the ESCAPE trial EVT group was excluded from the analysis (shown by the two crossed lines in [C]). Subtrees have been collapsed in (***b***) and (***c***) for better oversight. LVO = large vessel occlusion.

index stroke. In this model, patients were assigned to one out of 7 health states (mRS 0–6). Probabilities of these health states were based on the 90-day mRS distribution of patients in the ESCAPE trial EVT group, ESCAPE trial control group, and ESCAPE-LATE EVT group. This short-term model was followed by a long-run Markov state transition model with a cycle length of 12 months to estimate costs and outcomes over the patients' entire lifespan (up to 120 years). In the Markov model, patients could either maintain the same health status (the same mRS), suffer a recurrent stroke followed by either (a) recovery to the same mRS, or (b) deterioration to a worse/higher mRS, or (c) die due to age-related mortality or stroke survivor-specific mortality. We assumed a model starting age of 71.5 years, corresponding to the median age of the pooled patient sample.

All analyses in this study were conducted from two perspectives, as recommended by the Second Panel on Cost-Effectiveness in Health and Medicine[9] and the Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) guidelines (see checklist in the **s**upplement)[10]: the healthcare perspective, which only takes into account healthcare-related costs, and the societal perspective, which also considers costs to society outside the healthcare sector.

Model input parameters

Model probabilities
Probabilities of achieving a particular mRS state at 3 months in the short-run model were derived from the pooled ESCAPE/ESCAPE late time window patient sample. Probabilities for long term outcomes were based on results of large prospective cohort studies[11,12] and United States Life Tables,[13] as described in prior studies.[14,15] These long-term probabilities took recurrent stroke

risk, death, and post-stroke mRS changes into account. Utility weights from a prospective cohort study were used to translate mRS states into quality-adjusted life years (QALY).[16] Probabilities of receiving intravenous alteplase in each of the three groups (ESCAPE trial EVT group, ESCAPE trial control group, ESCAPE-LATE EVT group) were based on the observed intravenous alteplase usage in the pooled patient sample.

Since the number of patients in the two ESCAPE trial groups was small and the three patient groups were not been balanced in their baseline factors, in particular age and stroke severity, see (suppl. Table 1), which may influence the analysis results, we performed an unadjusted analysis, in which the observed mRS distributions of the groups were used as model input parameters, as well as an adjusted analysis, in which adjusted mRS probabilities for each of the three groups were used as input parameters (see Zerna et al [under review]). To do so, we derived probabilities for achieving a certain mRS category for each patient from a clustered multivariable ordinal logistic regression model with adjustment for the following prespecified variables: age, sex, baseline National Institutes of Health Stroke Scale (NIHSS) score, baseline Alberta Stroke Program Early CT Score (ASPECTS), occlusion location (internal carotid artery vs. M1 segment vs. M2 segment). Collateral status is another important baseline factor that determines patient outcome and that was available in the current study (suppl. Table 1). We deliberately chose not to adjust for ASPECTS and collateral status simultaneously for two reasons because collateral status was assessed on either single phase CTA or multiphase CTA in ESCAPE LATE, which may introduce some variability, and because ASPECTS and collateral status are collinear to some degree: patients with poorer collateral status are expected to have a lower ASPECTS and vice versa and thus, including both variables in the regression model may lead to multicollinearity.

Furthermore, since ESCAPE enrolled patients up to 12 hours while ESCAPE-LATE enrolled all patients after 6 hours without an upper time limit, we performed an additional sensitivity analysis in which only ESCAPE-LATE patients who presented between 6 and 12 hours from last known well were included and compared to ESCAPE trial patients presenting>6 hours from last known well.

Healthcare costs (U.S. data)

Estimated treatment costs were based on the National Inpatient Sample[17] and available literature.[14,15,18] The average cost of EVT was estimated at $15,510,[18] based on itemized hospital charges and summary bills.[18] Intravenous alteplase cost was estimated at $7,421, based on costs of hospital inpatient stays in the United States using the National Inpatient Sample, which describes costs by primary expected payer. Healthcare costs other than EVT and intravenous alteplase that were incorporated in the short-run model included supported discharge, rehabilitation, medication costs, and community care, which varied based on the degree of disability (i.e., the 90-day mRS).[18,19] All costs were inflated using the medical care component of the consumer price index on a yearly basis.[20]

Societal costs

Costs and cost-effectiveness of EVT in addition to best medical management compared with best medical management alone were assessed using the human capital approach. This included costs due to lost productivity (estimated from United States Bureau of Labor Statistics[20] age-specific employment rates[14,15] and age-adjusted mRS-specific return-to-work probabilities), informal care (unpaid caregiving provided by family and friends, estimated based on United States Census Bureau wages),[21] and costs due to stroke-related premature mortality and disability.[15]

Outcomes of interest

Costs were measured in US dollars, and effectiveness was measured in quality-adjusted life years (QALY).[9,22] To obtain lifetime QALYs for participants in each mRS category, life years were multiplied with mRS-specific utility measures.[16] All costs and QALYs were discounted by 3% each year.[9]

Cost-effectiveness of EVT in addition to best medical management was assessed using the incremental cost-effectiveness ratio (ICER):

$$\frac{(\text{Cost of EVT} + \text{best MM}) - (\text{Cost of best MM})}{(\text{QALYs of EVT} + \text{best MM}) - (\text{QALYs of best MM})}$$

$$= \frac{\text{Additional cost of EVT}}{\text{Gain in QALYs with EVT}}$$

Upper and lower willingness-to-pay (WTP) thresholds were set at $100,000 and $50,000, respectively.

We further calculated the mean net monetary benefit (NMB) and acceptability with respective 95% prediction intervals from probabilistic sensitivity analyses. The mean NMB is the difference between the product of the lifetime QALYs gained with EVT and the willingness to pay for 1 QALY minus the additional lifetime cost of EVT:

Net monetary benefit = (lifetime QALYs gained with EVT * willingness to pay for 1 QALY) – lifetime additional costs of EVT

Acceptability is the proportion of simulations in the probabilistic sensitivity analysis among all simulations that show cost-effectiveness of the treatment under investigation.

Analysis

The model structure is shown in Figure 1. The purpose of this study was to compare cost-effectiveness of EVT in addition to best medical care vs. best medical care only in (a) a randomized trial setting vs. (b) a "real-world" setting. Thus, while we used a single model with 3 arms, we performed two separate sets of analyses; one that compared lifetime costs and QALYs of late time window ESCAPE trial EVT group patients vs. ESCAPE trial control group patients (randomized trial setting), and one that compared lifetime costs and QALYs of ESCAPE-LATE EVT patients vs. ESCAPE trial control group patients ("real-world setting" in the sense that the ESCAPE-LATE patients were treated in clinical routine based on the discretion of the treating medical team and did not have to fulfill any specific EVT eligibility criteria). The groups that were not needed for comparison were excluded in the strategies' respective analyses (Fig. 1b,c).

In the base case analysis, lifetime QALYs gained, lifetime costs and the ICER were calculated using only model parameter point estimates, i.e. without assuming an underlying probability distribution of the parameters. In the probabilistic sensitivity analysis, each model parameter was assigned a distribution (see Suppl. Table 2), and 10,000 s order Monte Carlo simulations were performed for each analysis set, allowing for variation of each of the model parameters according to their assigned distribution simultaneously. Probabilistic sensitivity analysis results were visualized in scatter plots.

Results

After excluding patients presenting within 6 hours from last known well and patients with occlusions other than anterior circulation LVO, a total of 249 patients (mean age 71.5 years) were included in the final pooled patient sample (Suppl. Figure 1). The 90-day mRS probabilities of these patients served as input variables for the mRS probabilities in the short-run component of the unadjusted cost-effectiveness model.

Base case analysis – unadjusted analysis

In the clinical trial setting, late EVT in addition to best medical care resulted in increased lifetime QALYs and lower lifetime healthcare cost compared to best medical care only and was therefore the dominant strategy, both when analyzing the healthcare perspective and the societal perspective (Table 1). In the "real-world" setting, late EVT in addition to best medical care also resulted in increased lifetime QALYs and lower lifetime healthcare cost compared to best medical care only and was therefore the dominant strategy, both from a healthcare perspective and a societal perspective (Table 1). Both the gain in QALYs and cost savings with additional EVT were slightly higher in the real-world setting compared to the clinical trial setting (1.30 vs. 1.29 incremental QALYs, $21,219 vs. $13,457 [healthcare perspective]/ $21,921 vs. $13,724 [societal perspective] cost savings, see Table 1).

Base case analysis – adjusted analysis

When using mRS distributions that were adjusted for patient age, sex, baseline NIHSS, baseline ASPECTS and occlusion location instead of actually observed (unadjusted) mRS distributions for the

Table 1. Costs, QALYs gained and incremental cost-effectiveness ratios (ICER) with late time-window EVT in addition to best medical care vs. best medical care only (a) in a trial setting, and (b) in a real-world setting in the unadjusted analysis

	EVT with best medical care	Best medical care only	Difference
Trial setting (ESCAPE trial EVT group vs. ESCAPE trial control group)			
Cumulative lifetime QALYs gained	3.22	1.93	1.29
Cumulative lifetime costs (healthcare perspective) - $	133,180	150,509	−17,329
ICER (healthcare perspective) - $	EVT dominant		
Cumulative lifetime costs (societal perspective) - $	156,541	174,213	−17,673
ICER (societal perspective) - $	−13,724		
Real-world setting (ESCAPE-LATE EVT group vs. ESCAPE trial control group)			
Cumulative lifetime QALYs gained	3.23	1.93	1.30
Cumulative lifetime costs (healthcare perspective) - $	123,017	150,509	−27,492
ICER (healthcare perspective) - $	EVT dominant		
Cumulative lifetime costs (societal perspective) - $	145,813	174,213	−28,400
ICER (societal perspective) - $	−21,921		

EVT = endovascular treatment, QALY = quality-adjusted life year, ICER = incremental cost-effectiveness ratio.

Table 2. Costs, QALYs gained and incremental cost-effectiveness ratios (ICER) with late time-window EVT in addition to best medical care vs. best medical care only a) in a trial setting, and b) in a real-world setting in the adjusted analysis

	EVT with best medical care	Best medical care only	Difference
Trial setting (ESCAPE trial EVT group vs. ESCAPE trial control group)			
Cumulative lifetime QALYs gained	3.03	3.44	0.42
Cumulative lifetime costs (healthcare perspective) - $	135,768	113,623	22,144
ICER (healthcare perspective) - $	53,108		
Cumulative lifetime costs (societal perspective) - $	159,302	136,541	22,761
ICER (societal perspective) - $	54,582		
Real-world setting (ESCAPE-LATE EVT group vs. ESCAPE trial control group)			
Cumulative lifetime QALYs gained	3.08	3.03	0.05
Cumulative lifetime costs (healthcare perspective) - $	132,425	113,623	18,802
ICER (healthcare perspective) - $	357,527		
Cumulative lifetime costs (societal perspective) - $	155,874	136,541	19,333
ICER (societal perspective) - $	367,637		

Adjusted mRS probabilities were derived from multivariable ordinal logistic regression models (adjusted for patient age, sex, baseline NIHSS, baseline ASPECTS and occlusion location).
EVT = endovascular treatment, QALY = quality-adjusted life year.

three groups, and when considering the clinical trial setting, late EVT resulted in slightly more lifetime QALYs (3.44 vs. 3.03) and higher lifetime cost compared to best medical care only from a healthcare perspective (ICER 53,108) and a societal perspective (ICER 54,582, Table 2). In the "real-world setting", lifetime QALYs were marginally higher with late EVT (3.08 vs. 3.03) and lifetime costs were also higher from a healthcare perspective (ICER 357,527) and a societal perspective (ICER 367,637, Table 2).

Sensitivity analysis in patients presenting between 6-12 hours from last known well

One-hundred-twenty-nine of 200 ESCAPE-LATE patients and all included ESCAPE patients presented between 6 and 12 hours from last known well. When only including these patients in the analysis,

real-world EVT (ie, comparing ESCAPE-LATE patients presenting within 6–12 hours from last known well to ESCAPE control arm patients presenting within 6–12 hours from last known well) was the dominant strategy in the unadjusted analysis and cost effective in the adjusted analysis, both from a healthcare and a societal perspective (ICER 42,700 and 39,529 respectively, see Suppl. Table 3).

Unadjusted probabilistic sensitivity analysis

In the unadjusted probabilistic sensitivity analysis (10,000 s order Monte Carlo simulations), mean NMBs at the upper and lower WTP thresholds were consistently higher for late EVT in addition to best medical care, both in the clinical trial setting and the "real-world" setting, and both from the healthcare and the societal

perspective (Suppl. Table 4). Mean NMB of additional late EVT were higher in the real-world setting compared to the clinical trial setting. Acceptability of late EVT was > 96% in all scenarios, and slightly higher in the real-world setting than in the clinical trial setting. Furthermore, acceptability was minimally higher in the healthcare perspective analyses compared to the societal perspective analyses (Suppl. Table 4). Unadjusted cost-effectiveness scatter plots for the clinical trial setting and "real-world" setting are shown in Figure 2a,b.

Adjusted probabilistic sensitivity analysis

In the adjusted probabilistic sensitivity analysis, the mean NMB was higher for EVT vs. best medical care only for patients in the randomized trial setting, with EVT acceptability ranging between 51% and 62%, depending on the perspective taken and WTP threshold used (Suppl. Table 5). Mean NMB was lower for EVT vs. best medical care only in the "real-world" setting, with EVT acceptability ranging between 33% and 43% (Suppl. Table 5). Adjusted cost-effectiveness scatter plots for the clinical trial setting and "real-world" setting are shown in Figure 2c,d.

Discussion

In usual care ("real-world" setting), the cost-effectiveness of late-window EVT is highly dependent upon patient selection. EVT in addition to best medical care for LVO patients presenting beyond 6 hours from last known well was cost-effective and even cost-saving when using unadjusted 90-day clinical outcomes from the ESCAPE trial and the ESCAPE-LATE study. However, "real-world" EVT patients in ESCAPE had more favorable baseline characteristics compared to the ESCAPE trial groups, and after adjusting for these differences in baseline status, the health economic late EVT benefit was reduced in the trial setting, and no late EVT benefit was seen in the real-world setting.

Clearly, not all LVO patients presenting in the late time window benefit from EVT. Therefore, the randomized DAWN and DEFUSE-3 trials have applied a number of clinical and imaging eligibility criteria and mandated advanced imaging with CT perfusion or MRI(1, 2), and by doing so, they were able to provide proof-of-principle that late time window EVT can be beneficial in some patients. Recently, the MR CLEAN-LATE trial showed that patients can also be selected for late time window EVT with less restrictive selection criteria based on CTA.[23]

Our study showed that EVT is cost-effective in late time window patients that were selected for EVT by the treating medical team in clinical routine; in fact, the health economic benefit was even slightly larger compared to a clinical trial setting. However, patients selected in clinical routine had more favorable baseline characteristics than the comparator groups from the ESCAPE trial, which may imply that physicians intuitively incorporate baseline factors into their treatment decisions and only offer EVT to those late time window patients with a favorable baseline profile. After accounting for these baseline characteristics between the groups, EVT was marginally cost-effective in the randomized trial setting, and not cost-effective in the "real-world setting" any more. Ultimately, whether late time window EVT is cost-effective or not is mainly dependent on patient selection. The unadjusted analysis in this study reflects how physicians select late time window patients for EVT in clinical practice: those who are selected for EVT

had better baseline characteristics, and this resulted in EVT being cost-effective in the unadjusted analysis, while no such health economic benefit was seen after adjustment for baseline factors. Therefore, our findings suggest that only when selecting patients with a favorable baseline profile is late time window real-world EVT cost-effective (unadjusted analysis), while unselected late time window EVT in all patients is not (adjusted analysis). A previous publication by Gao et al also suggests that some form of patient selection for late time window EVT is needed, as it showed that late time window EVT in the "real-world" in the Australian healthcare setting was only cost-effective in patients fulfilling the DAWN and DEFUSE-3 trial criteria(7). EVT in DAWN/ DEFUSE-3 ineligible patients on the other hand resulted in decreased QALYs (−1.43 QALY/ −1.02 QALY) and higher costs (AUD9,271/8,955).

In the present study, clinician-based late time window patient selection for EVT also resulted in less health economic benefit compared to trial patients. This diminishing benefit compared to the randomized trial sample may be due to the less structured patient selection in real- world practice, but could also be related to the fact that patients in clinical trials probably receive overall better care (Hawthorne-effect).[24]

Limitations

Our results have several limitations. First, patients in ESCAPE-LATE were treated > 6h from last known well, without any upper time limit, while the historical controls from the ESCAPE trial presented between 6 and12 hours from last known well, since the trial allowed enrolment only up to 12-hours; i.e. the time since last known well differed systematically between the two studies in a way that favored the ESCAPE groups. Furthermore, we also found significant differences in baseline NIHSS and collateral score. Second, the 90-day mRS, which was used to estimate initial mRS probabilities in the short run model component, was assessed blinded to treatment allocation in ESCAPE, and unblinded in ESCAPE LATE. Third, ESCAPE LATE patients were treated after ESCAPE had finished enrolment, and thus, EVT techniques may have been more refined during the ESCAPE-LATE enrolment period. Fourth, the number of historical controls from the ESCAPE trial was small. Fifth, the proportion of late-time window patient in the best medical care group receiving intravenous thrombolysis was higher than what would be expected in clinical routine (55.0%), which may have biased the results towards better 90-day mRS in this group. Sixth, this cost-effectiveness analysis was performed using a United States perspective and cannot be generalized to other countries. Lastly, cost-effectiveness models are built on numerous assumptions and should be interpreted with caution, since healthcare and particularly societal costs are challenging to measure and may vary substantially even within one country.

Conclusion

In this health economic evaluation, EVT in addition to best medical care for LVO patients presenting beyond 6 hours from last known well was cost-effective and even cost-saving in the clinical trial setting and "real-world" setting, although this was largely related to differences in baseline characteristics that favored the "real-world" EVT group. After adjusting for these differences, EVT benefit was reduced in the trial setting, and no EVT benefit was seen in the real-world setting.
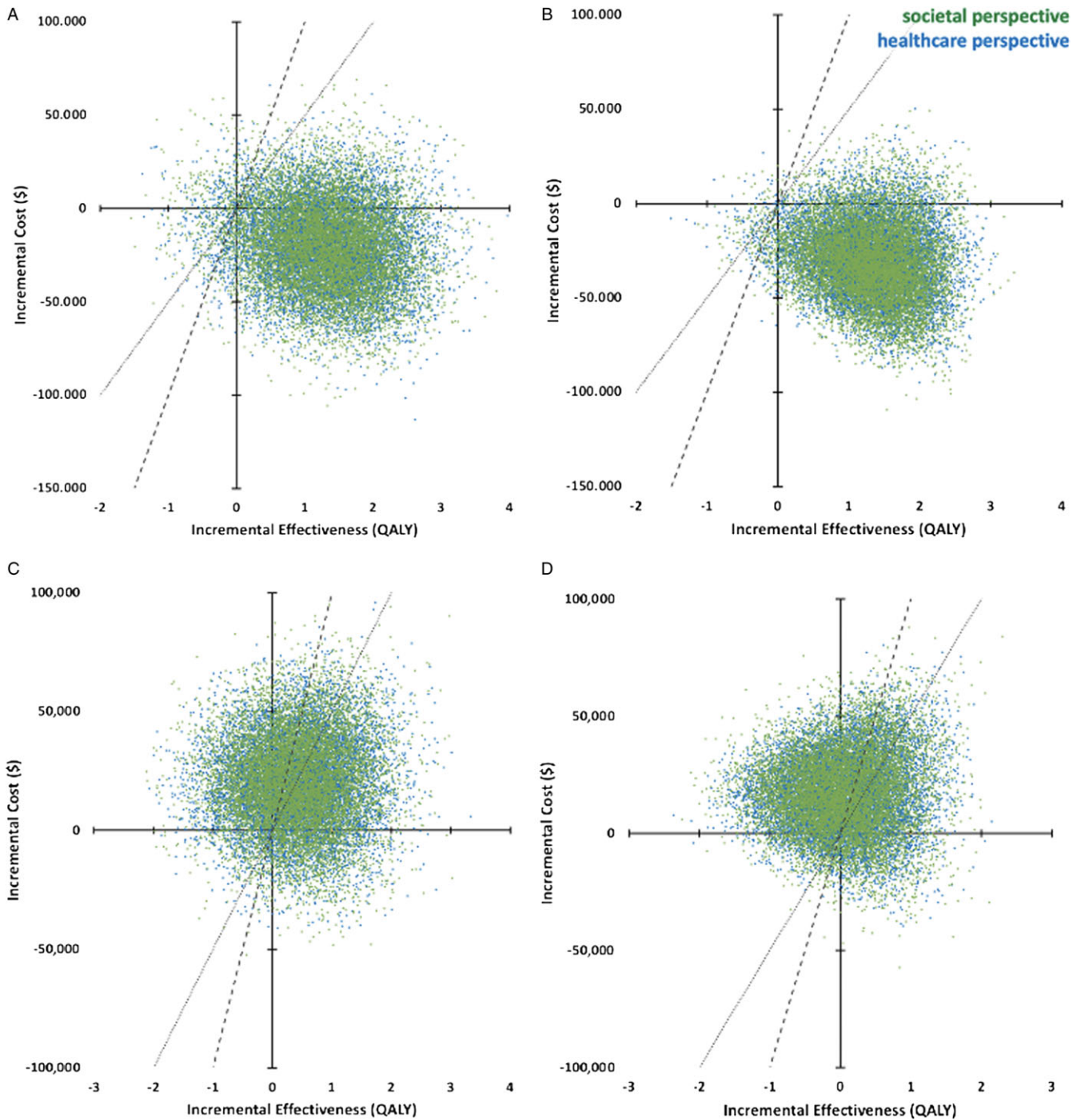
Figure 2. Probabilistic sensitivity analysis (10,000 Monte Carlo simulations) illustrating incremental cost per quality-adjusted life year (QALY) gained of EVT in addition to best medical care in anterior circulation large vessel occlusion stroke patients presenting>6 hours from last known well compared to best medical care alone from a United States societal perspective (green dots) and healthcare perspective (blue dots). Each dot represents the result from a single Monte Carlo simulation. Dashed lines indicate $50,000/QALY willingness to pay thresholds, and dotted lines indicate $100,000/QALY willingness to pay thresholds. (*a*) shows unadjusted results for a clinical trial setting (based on data from the late time window ESCAPE trial endovascular treatment (EVT) group and the late time window ESCAPE trial control group). (*b*) shows unadjusted results for the "real-world" setting (based on data from the late time window ESCAPE-LATE EVT group and the late time window ESCAPE trial control group). (*c*) shows results for a clinical trial setting (based on data from the late time window ESCAPE trial EVT group and the late time window ESCAPE trial control group). (*d*) shows results for the "real-world" setting (based on data from the late time window ESCAPE-LATE EVT group and the late time window ESCAPE trial control group). Adjustment was performed for patient age, sex, baseline NIHSS, baseline ASPECTS, and occlusion location.

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