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Endovascular Thrombectomy Alone for Large Vessel Occlusion: A Cost-Effectiveness Evaluation Based on Meta-Analyses

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BACKGROUND: The benefit of intravenous thrombolysis with alteplase before endovascular thrombectomy (EVT) for acute ischemic stroke due to large vessel occlusion remains debated. In this study, we analyzed the cost-effectiveness of EVT alone versus intravenous alteplase before EVT in patients directly admitted to EVT-capable stroke centers from the Dutch health care payer perspective.

METHODS: A decision analysis was performed using a Markov model with 15-year simulated follow-up to estimate total costs, quality-adjusted life years, and an incremental cost-effectiveness ratio of intravenous alteplase before EVT compared with EVT alone. A hypothetical cohort of 10 000 patients with large vessel occlusion aged 70 years was run in Monte Carlo simulation. Functional outcome of each treatment was derived from pooled results of 6 randomized controlled trials (RCTs). Uncertainty was assessed by probabilistic analyses, scenario analyses, and 1-way sensitivity analyses.

RESULTS: Using functional outcomes obtained from 6 RCTs (intention-to-treat population), intravenous alteplase before EVT resulted in 0.05 quality-adjusted life years gained at an additional $2817 compared with EVT alone, resulting in the incremental cost-effectiveness ratio of $62 287. Probabilistic analyses showed that intravenous alteplase before EVT had a probability of 45% and 54%, respectively, of being cost-effective at the $52 500 and $84 000 thresholds. Restricting functional outcomes from our post hoc modified as-treated analysis of 6 RCTs (scenario 1), European RCTs (scenario 2), or a Dutch RCT (scenario 3), intravenous alteplase before EVT was cost-effective in 64%, 81%, and 50% of simulations at the $52 500 threshold, and 79%, 91%, and 67% of simulations at the $84 000 threshold.

CONCLUSIONS: Intravenous alteplase before EVT was not cost-effective in patients with large vessel occlusion in the Netherlands at the $52 500 threshold but possibly cost-effective at the $84 000 threshold. Variable functional outcomes at 3 months based on different trial populations affected the cost-effectiveness of intravenous alteplase before EVT.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: health care costs ■ quality-adjusted life years ■ stroke ■ thrombectomy ■ tissue-type plasminogen activator

Both intravenous thrombolysis (IVT) with alteplase and endovascular thrombectomy (EVT) have become the standard of care for patients with acute ischemic stroke due to large vessel occlusion (LVO). The added benefit of alteplase before EVT is currently debated as alteplase appeared to be less effective in achieving

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Nonstandard Abbreviations and Acronyms

EVT	endovascular thrombectomy
ICER	incremental cost-effectiveness ratio
IVT	intravenous thrombolysis
LVO	large vessel occlusion
mRS	modified Rankin Scale
QALY	quality-adjusted life year
RCT	randomized controlled trial
WTP	willingness-to-pay

reperfusion in case of LVO, especially in EVT-capable centers where patients could be treated directly with EVT. Also, it could increase the risk of intracranial hemorrhage. Recently, 6 randomized controlled trials (RCTs) were performed to answer this question.[1–6] Two RCTs performed in China (DIRECT-MT [Direct Intra-Arterial Thrombectomy in Order to Revascularize Acute Ischemic Stroke Patients With LVO Efficiently in Chinese Tertiary Hospitals][5] and DEVT [Direct EVT vs Combined IVT and EVT for Patients With LVO in the Anterior Circulation][6]) demonstrated that EVT alone was not worse than IVT before EVT. However, other trials such as SKIP[4] ([Direct Mechanical Thrombectomy in Acute LVO Stroke]; Japan), MR CLEAN-NO IV[2] ([Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands Investigating the Added Benefit of Intravenous Alteplase Before Thrombectomy]; the Netherlands), SWIFT-DIRECT[1] ([Solitaire With the Intention for Thrombectomy Plus Intravenous t-PA Versus DIRECT Solitaire Stent-Retriever Thrombectomy in Acute Anterior Circulation Stroke]; Europe and Canada), and DIRECT-SAFE[3] ([Randomized Controlled Trial of DIRECT Endovascular Clot Retrieval Versus Standard Bridging Thrombolysis With Endovascular Clot Retrieval Within 4.5 Hours of Stroke Onset]; Australia, New Zealand, China, and Vietnam) could not rule out a potential worse outcome of EVT alone. A recent patient-level meta-analysis including over 2000 patients[7] did not exclude a possible loss of clinical effect after omitting IVT. Hence, associated costs of treatments and long-term consequences play an important role to support decision-making as physicians might be hesitant to withhold intravenous alteplase before EVT.

Previous cost-effectiveness studies using modified Rankin Scale (mRS) outcomes from DIRECT-MT[5] showed that EVT alone was dominant in the Chinese[8] and US settings.[9] Whether EVT alone might be considered the dominant strategy in European health care settings with different willingness-to-pay (WTP) thresholds, drug costs, and health care costs after stroke remains a relevant policy question. Therefore, we aimed to assess the cost-effectiveness of EVT alone compared with intravenous alteplase before EVT in patients with LVO admitted directly to EVT-capable centers in the Netherlands.

METHODS

Data Availability

The authors declare that all supporting data are available within the article and its Supplemental Material.

Study Cohort and Setting

A hypothetical cohort of 10 000 patients undergoing EVT alone or intravenous alteplase before EVT was simulated to estimate the total costs and quality-adjusted life years (QALYs). The cohort included patients with acute ischemic stroke with LVO receiving intravenous alteplase (0.9 mg/kg) before EVT or EVT alone, who were presented directly to EVT-capable stroke centers within 4.5 hours after symptom onset. Based on a previous meta-analysis of 6 RCTs,[7] the average age in this cohort was 71 years, and 55.7% of patients were male. In line with the MR CLEAN-NO IV[2] results, we used a median alteplase dose of 70 mg, implying an average weight of 78 kg.

Model Structure

A Monte Carlo simulation using a decision tree and Markov model was performed to estimate the cost-effectiveness of EVT alone compared with intravenous alteplase before EVT using the Dutch health care payer perspective. The conceptual model was adopted and adjusted from previously published models.[10,11] Patients with LVO were admitted to EVT-capable stroke centers to receive EVT alone or intravenous alteplase before EVT (Figure 1A). Each treatment resulted in a different level of disability represented by the mRS distribution at 90 days in the RCTs, with a higher score indicating more severe disability. In the model, we considered 5 health states: mRS scores of 0 to 1 (excellent outcome), 2 to 3 (slight or moderate disability), 4 (moderately severe disability), 5 (severe disability), and 6 (death). Although mRS scores of 3, 4, 5, and 6 are usually grouped as nonfunctional independence in clinical trials, mRS score 3 status was shown to be more similar to mRS score 2 than to mRS score 4 in terms of health-related quality of life.[12] A decision tree was used to allocate patients into the Markov model and capture costs and QALYs of each treatment during the first year. Next, we used a Markov model to extrapolate the costs and QALYs after the first year. We assumed that patients could improve, remain stable, or deteriorate in their mRS score during the first 5 years but could only remain stable or deteriorate on their mRS score afterward (Figure 1B and 1C). For example, patients with mRS scores of 2 to 3 could stay in mRS score 2 to 3 or make a transition to mRS scores of 0 to 1, 4, and 5 or death in 1-year cycles in the first 5 years. The time horizon was set at 15 years as average life expectancy in the Dutch 70-year-old population is 16 years.[13] The model was built in Treeage Pro 2022 R1.2.

Model Parameters

mRS at 90 Days and Transition Probabilities

We identified 6 relevant RCTs based on a recently published systematic review[7]: (1) DIRECT-MT,[5] (2) MR CLEAN-NO IV,[2] (3)

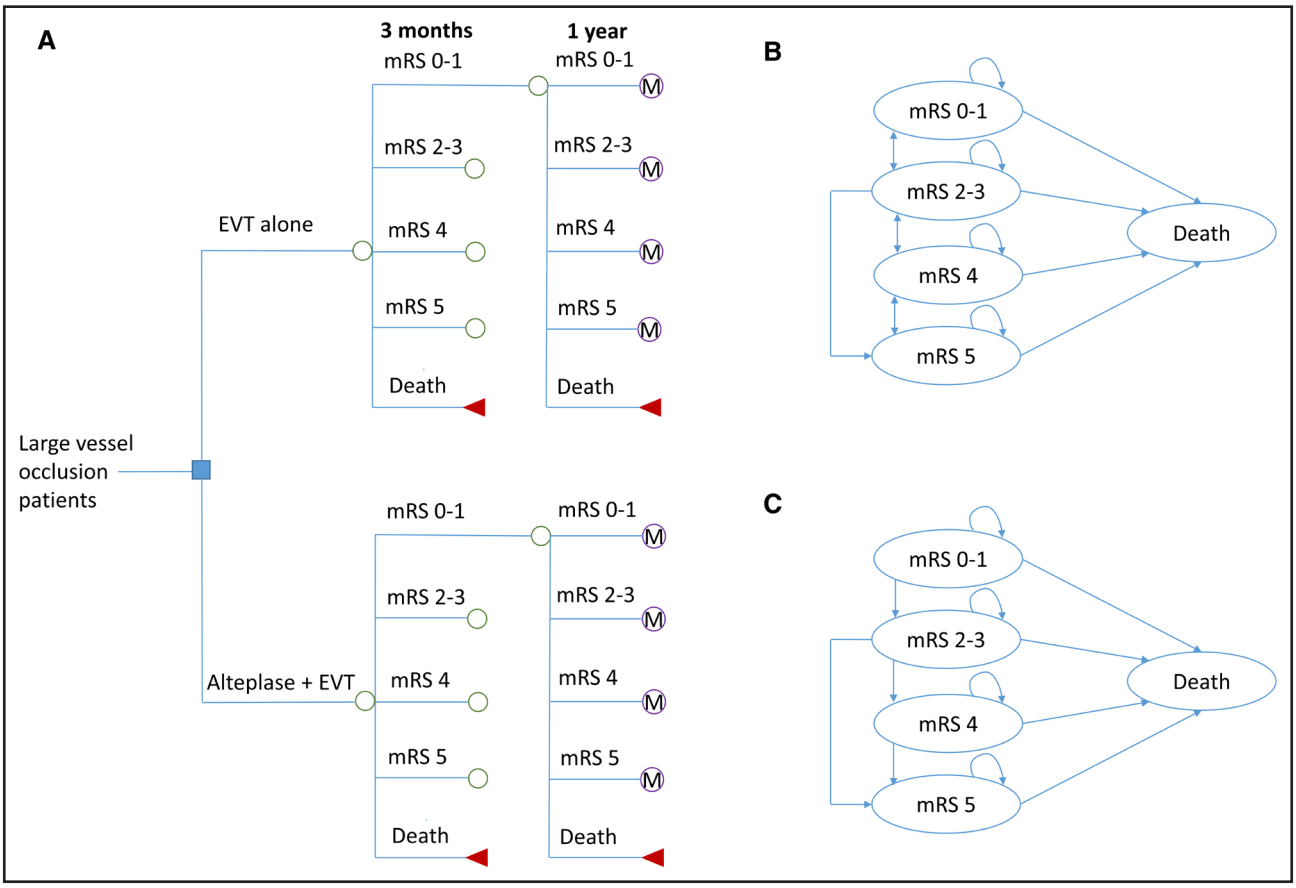

Figure 1. Model structure.
A, Decision tree model. **B**, Markov model from 1 to 5 years. **C**, Markov model from 5 to 15 years. EVT indicates endovascular thrombectomy; M, Markov model; and mRS, modified Rankin Scale.

SKIP,[4] (4) DEVT,[6] (5) SWIFT-DIRECT,[1] and (6) DIRECT-SAFE.[3] In the base case analysis, we used published mRS distributions from the patient-level meta-analysis of these 6 RCTs (intention-to-treat group[7]; Table 1). Transition probabilities from 90 days to 1 year and for each 1-year cycle afterward in the Markov model were derived from the 2-year follow-up of the MR CLEAN trial ([Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands]; Table S1).[14] Mortality data per age and sex were derived from the Royal Dutch Actuarial Association[15] (Tables S2 and S3).

Costs and Utilities

Utility scores of Dutch patients with AIS were obtained from a previous cost-effectiveness study conducted in the Netherlands.[16] As we used a health care payer perspective, only direct medical costs were included (Table 2). The median received dose of alteplase in MR CLEAN-NO IV[2] was used to calculate IVT costs. Alteplase costs were obtained from the Healthcare Institute in the Netherlands.[17] The EVT costs were copied from a recently published Dutch study.[11] In the base case analysis, the proportion of patients who underwent IVT or EVT in each group was used from the meta-analysis of 6 RCTs.[7] We assumed that medical costs other than IVT and EVT costs were similar between the 2 groups, that is, emergency medical services and adverse events. Annual costs after stroke, including the first year, the second year, and the years then onward, were derived from a previous Dutch study.[16] In the model, we used annual costs during the first year rather than dividing costs into 90 days and the following 9 months. All costs were converted to the reference year of 2022 using the Dutch consumer price index[19] and expressed in US dollars (€1=$1.05 in 2022).[20]

Cost-Effectiveness Analysis

The annual discount rate for costs and QALYs was set at 4% and 1.5%, respectively, as recommended by the Dutch health economics guidelines.[18] The main outcome measures included total costs, QALYs, and incremental cost-effectiveness ratios (ICERs). The ICER was used to assess the cost-effectiveness of 2 treatments and was calculated as follows: $ICER=(cost_{alteplase+EVT}-cost_{EVT})/(QALY_{alteplase+EVT}-QALY_{EVT})$. In the Netherlands, the WTP thresholds vary from €20 000 per QALY to the highest threshold of €80 000 per QALY based on the disease burden. We used the iMTA tool[21] to derive the WTP thresholds of €50 000 ($52 500) and €80 000 ($84 000) used in this study. If the ICER is less than the WTP threshold, intravenous alteplase before EVT is cost-effective. In the probabilistic analyses, Monte Carlo simulations of 10 000 iterations generated a mean output based on distributions of input parameters (Tables 1 and 2; Table S4) and assessed the probability of being cost-effective of each treatment at

Table 1. mRS Distributions at 90 Days

Strategy	Base case: whole RCTs (6 RCTs,* intention to treat)	Scenario 1: whole RCTs (6 RCTs,* post hoc modified as treated)	Scenario 2: European RCTs (2 RCTs,† intention to treat)	Scenario 3: Dutch RCT (MR CLEAN-NO IV, intention to treat)
EVT alone: number of patients, %				
mRS score of 0–1	344 (29.89%)	292 (28.35%)	123 (25.95%)	44 (16.12%)
mRS score of 2–3	395 (34.32%)	350 (33.98%)	185 (39.03%)	117 (42.86%)
mRS score of 4	118 (10.25%)	109 (10.58%)	46 (9.70%)	26 (9.52%)
mRS score of 5	112 (9.73%)	103 (10.00%)	42 (8.86%)	30 (10.99%)
mRS score of 6	182 (15.81%)	176 (17.09%)	78 (16.46%)	56 (20.51%)
Distribution	Dirichlet‡ (344;395;118;112;182)	Dirichlet‡ (292;350;109;103;176)	Dirichlet‡ (123;185;46;42;78)	Dirichlet‡ (44;117;26;30;56)
Intravenous alteplase+EVT: number of patients, %				
mRS score of 0–1	354 (30.54%)	271 (28.68%)	130 (27.48%)	41 (15.41%)
mRS score of 2–3	393 (33.91%)	341 (36.08%)	199 (42.07%)	120 (45.11%)
mRS score of 4	125 (10.79%)	107 (11.32%)	50 (10.57%)	38 (14.29%)
mRS score of 5	115 (9.92%)	99 (10.48%)	35 (7.40%)	25 (9.40%)
mRS score of 6	172 (14.84%)	127 (13.44%)	59 (12.47%)	42 (15.79%)
Distribution	Dirichlet‡ (354;393;125;115;172)	Dirichlet‡ (271;341;107;99;127)	Dirichlet‡ (130;199;50;35;59)	Dirichlet‡ (41;120;38;25;42)

EVT indicates endovascular thrombectomy; mRS, modified Rankin Scale; and RCT, randomized controlled trial.

*DIRECT-MT (Direct Intra-Arterial Thrombectomy in Order to Revascularize Acute Ischemic Stroke Patients With LVO Efficiently in Chinese Tertiary Hospitals), DEVT (Direct EVT vs Combined IVT and EVT for Patients With LVO in the Anterior Circulation), SKIP (Direct Mechanical Thrombectomy in Acute LVO Stroke), MR CLEAN-NO IV (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands Investigating the Added Benefit of Intravenous Alteplase Before Thrombectomy), SWIFT-DIRECT (Solitaire With the Intention for Thrombectomy Plus Intravenous t-PA Versus DIRECT Solitaire Stent-Retriever Thrombectomy in Acute Anterior Circulation Stroke), and DIRECT-SAFE (Randomized Controlled Trial of DIRECT Endovascular Clot Retrieval Versus Standard Bridging Thrombolysis With Endovascular Clot Retrieval Within 4.5 Hours of Stroke Onset).

†MR CLEAN-NO IV and SWIFT-DIRECT.

‡Parameter means of Dirichlet distribution were equivalent to the sample size of each mRS category in RCTs.

the varying WTP thresholds. The study was reported according to the Consolidated Health Economic Evaluation Reporting Standards statement.[22]

Scenario Analysis

In addition to our base case analysis (mRS distribution based on 6 RCTs, intention-to-treat analysis), we analyzed the cost-effectiveness of EVT alone versus intravenous alteplase before EVT in 3 additional scenarios where mRS distributions at 90 days were varied and derived from (1) post hoc modified as-treated analysis from 6 RCTs; (2) European RCTs (MR CLEAN-NO IV and SWIFT-DIRECT, intention-to-treat analysis); and (3) Dutch RCT (MR CLEAN-NO IV, intention-to-treat analysis; Table S4). In scenario 1, we applied the mRS distributions of post hoc modified as-treated analysis from 6 RCTs,[7] which included patients who actually received IVT in the IVT+EVT group, and did not receive IVT in the EVT alone group, irrespective of randomization arm. Patients with missing data or patients who received rescue IVT were excluded.[7] We calculated the percentage of patients with mRS 4 and mRS 5 based on the ratio in the intention-to-treat analysis due to unavailable data of mRS scores of 4 and 5 in the post hoc modified as-treated analysis. Scenario 2 was designed specifically for using mRS distributions at 90 days from the European RCTs, based on the study-level meta-analysis from MR CLEAN-NO IV and SWIFT-DIRECT, although 8 patients were recruited from Canada in SWIFT-DIRECT (8/408 patients). For scenario 3, we used mRS distributions at 90 days from MR CLEAN-NO IV conducted in the Netherlands (Table 1).

One-Way Sensitivity Analysis

One-way deterministic sensitivity analyses were performed to identify 15 parameters with a high effect on the ICER by changing parameters one by one. In 1-way deterministic sensitivity analysis, parameters varied over a plausible range from 95% CIs as the high and low boundaries or a range of 20% from base case values (Table 2). Values of mRS scores in 1-way deterministic sensitivity are described in Table S5.

Model Validation

We assessed model validation in terms of the conceptual model, input data, computerized model, and operation according to the Assessment of the Validation Status of Health-Economic decision models tool[23] (Table S6). The simulated mRS distributions were compared with mRS distributions from MR CLEAN[14] and other cohorts[24,25] (Figures S1 through S6).

Ethics Approval

No ethics approval was required as all data were derived from published literature.

RESULTS

Base Case Analysis

In the base case analysis, intravenous alteplase before EVT was more costly ($2817 extra) yet yielded 0.05 QALY improvement per patient compared with EVT alone,

Table 2. Model Parameters

Input parameter	Value	1-way sensitivity analysis	Distribution	Source
%Male	55.7%	95% CI, 53.7%–57.7%	β (α=1289; β=1026)	IRIS study[7]
%IVT in the EVT-alone group	3.5%	95% CI, 2.4%–4.5%	β (α=41; β=1114)	IRIS study[7]
%IVT in the IVT+EVT group	97.9%	95% CI, 97.1%–98.8%	β (α=1137; β=25)	IRIS study[7]
%EVT in the EVT-alone group	97.1%	95% CI, 96.2%–98.1%	β (α=1121; β=34)	IRIS study[7]
%EVT in the IVT+EVT group	97.2%	95% CI, 96.3%–98.2%	β (α=1129; β=33)	IRIS study[7]
Utility values		±20%	β (α; β)	Dutch study[16]
mRS score of 0–1	0.94		β (5.61; 0.36)	
mRS score of 2–3	0.72		β (2.28; 0.89)	
mRS score of 4	0.41		β (1.06; 1.52)	
mRS score of 5	0.20		β (0.31; 1.25)	
mRS score of 6	0.00	Invariant	Invariant	
Costs*				
IVT with alteplase†	$1224	±20%	Uniform (±20%)	Drug cost,[17] Dutch reference costs[18]
EVT	$12 017	±20%	Uniform (±20%)	Dutch study[11]
Costs in year 1		±20%	λ (α; λ)	Dutch study[16]
mRS score of 0–1	$37 748		λ (1.09; 2.90×10^{-5})	
mRS score of 2–3	$76 721		λ (3.21; 4.18×10^{-5})	
mRS score of 4	$127 041		λ (9.87; 7.77×10^{-5})	
mRS score of 5	$109 215		λ (10.06; 9.21×10^{-5})	
mRS score of 6	$23 860		λ (1.48; 6.21×10^{-5})	
Costs in year 2		±20%	λ (α; λ)	Dutch study[16]
mRS score of 0–1	$6706		λ (0.14; 2.07×10^{-5})	
mRS score of 2–3	$14 262		λ (0.61; 4.31×10^{-5})	
mRS score of 4	$48 813		λ (0.90; 1.83×10^{-5})	
mRS score of 5	$63 766		λ (5.41; 8.49×10^{-5})	
mRS score of 6	$478		λ (0.02; 3.67×10^{-5})	
Costs in year 3 and then onward		±20%	λ (α; λ)	Dutch study[16]
mRS score of 0–1	$4105		λ (0.16; 3.89×10^{-5})	
mRS score of 2–3	$12 131		λ (0.61; 5.05×10^{-5})	
mRS score of 4	$35 076		λ (2.43; 6.92×10^{-5})	
mRS score of 5	$62 153		λ (4.89; 7.87×10^{-5})	
mRS score of 6	$423		λ (0.01; 3.41×10^{-5})	

EVT indicates endovascular thrombectomy; IRIS, Improving Reperfusion strategies for Ischemic Stroke; IVT, intravenous thrombolysis; and mRS, modified Rankin Scale.

*Costs were reported at the year 2022.

†Including alteplase 50 mg, alteplase 20 mg, personnel cost, and 44% of overhead cost rate.

leading to the ICER of $62 287 per QALY (Table 3). The results of probabilistic sensitivity analysis showed that 45% and 54% of simulations indicated cost-effective at thresholds of $52 500 and $84 000, respectively. However, simulations were scattered in the northeast (higher costs, higher QALYs) and northwest (higher costs, lower QALYs) quadrants, which implies considerable uncertainty of incremental QALYs between intravenous alteplase before EVT and EVT alone (Figure 2).

Scenario Analysis

In scenario 1 (post hoc modified as-treated analysis from 6 RCTs), intravenous alteplase before EVT produced an additional cost of $7535 and additional QALY of 0.20, resulting in an ICER of $38 139 per QALY. The probability of cost-effectiveness for intravenous alteplase before EVT was 64% and 79% at thresholds of $52 500 and $84 000. Similar trends were obtained when mRS distributions at 90 days were derived from the European RCTs (scenario 2) or the Dutch RCT (scenario 3). In scenario 2, intravenous alteplase before EVT was cost-effective compared with EVT alone, with an ICER of $26 087 per QALY. The probability of intravenous alteplase before EVT being cost-effective was 81% and 91% at thresholds of $52 500 and $84 000. In scenario 3, intravenous alteplase before EVT resulted in additional costs

Table 3. Probabilistic Model Results (per Patient)

	Total cost	Incremental cost	QALYs	Incremental QALY	ICER ($/QALY)	Percentage of being cost-effective at $52 500	Percentage of being cost-effective at $84 000
Base case: whole RCTs (6 RCTs, intention to treat)							
EVT alone	$151 188	…	5.07	…	…	55%	46%
IV alteplase+EVT	$154 005	$2817	5.12	0.05	62 287	45%	54%
Scenario 1: whole RCTs (6 RCTs, post hoc modified as treated)							
EVT alone	$149 489	…	4.95	…	…	36%	21%
IV alteplase+EVT	$157 024	$7535	5.15	0.20	38 139	64%	79%
Scenario 2: European RCTs (2 RCTs, intention to treat)							
EVT alone	$151 580	…	5.07	…	…	19%	9%
IV alteplase+EVT	$160 641	$9061	5.41	0.45	26 087	81%	91%
Scenario 3: Dutch RCT (MR CLEAN-NO IV, intention to treat)							
EVT alone	$144 604	…	4.56	…	…	50%	33%
IV alteplase+EVT	$157 671	$13 068	4.84	0.27	47 778	50%	67%

EVT indicates endovascular thrombectomy; ICER, incremental cost-effectiveness ratio; IV, intravenous; MR CLEAN-NO IV, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands Investigating the Added Benefit of Intravenous Alteplase Before Thrombectomy; QALY, quality-adjusted life year; and RCT, randomized controlled trial.

($13 068) while gaining more QALYs (0.27 QALYs), with 50% and 67% probability of being cost-effective at the $52 500 and $84 000 thresholds. Intravenous alteplase before EVT in 3 scenarios had higher probabilities of being cost-effective compared with the base case (Figure 3; Figures S7 through S9).

One-Way Sensitivity Analysis

In the 1-way sensitivity analysis, the proportion of mRS scores 4 and 5 had the most impact on ICERs of intravenous alteplase before EVT versus EVT alone (Figure S10).

DISCUSSION

This study showed that intravenous alteplase before EVT did not appear cost-effective compared with EVT alone in patients with LVO admitted directly to EVT-capable centers at the $52 500 threshold (45% probability of cost-effectiveness). However, at the $84 000 threshold, intravenous alteplase before EVT had 54% probability of cost-effectiveness. When we applied pooled mRS distributions from post hoc modified as-treated analysis from 6 RCTs (scenario 1), the European RCTs (scenario 2), or the Dutch RCT (scenario 3), intravenous alteplase before EVT was likely cost-effective at both of the $52 500 and $84 000 thresholds. Factors related to different settings[26] may have contributed to the differences in the cost-effectiveness results between European and Asian RCTs. For example, in accordance with local guidelines, alteplase 0.6 mg/kg was used for patients with LVO in Japan[4] compared with 0.9 mg/kg in other clinical trials. Time from onset to IVT also varied between RCTs[7]; 185 minutes in DIRECT-MT, 169 minutes in DEVT, 159 minutes in DIRECT-SAFE, 145 minutes in SWIFT-DIRECT, 143 minutes in SKIP, and 98 minutes in MR CLEAN-NO IV. In DIRECT-MT[5] and DEVT[6] performed in China, written informed consent was obtained before randomization. In addition, Chinese patients were required to pay for IVT out of pocket. These processes may well have caused a delay in alteplase administration compared with other settings, for example, compared with the deferred consent procedure in MR CLEAN-NO IV[2] and in emergency circumstances in SWIFT-DIRECT.[1] Recently, better functional outcomes of IVT before EVT were observed in patients with LVO with a time from onset to IVT of ≤2 hours compared with EVT alone.[27] Therefore, when mRS distributions were derived from RCTs with shorter time from onset to IVT (scenarios 2 and 3), intravenous alteplase before EVT showed the higher probability of being cost-effective compared with the base case. Additionally, LVO confirmation by a computed tomography angiogram was required before IVT administration in RCTs, which could have led to delayed administration of IVT. This may not be generalizable to the Dutch clinical practice, as EVT-capable centers in the Netherlands usually deliver rapid IVT administration after review of the noncontrast computed tomography to rule out hemorrhage.

Interestingly, our results contradict some previous economic evaluation studies.[8,9,28] Cost-effectiveness studies in the United States[9,28] and China[8] imply that EVT alone was the preferred treatment from a health economic viewpoint, resulting in higher QALYs (0.01– 0.77) and cost savings ($1707–$60 535 per patient). Our results do not support these findings as EVT alone reduced both costs ($2817–$13 068) and QALYs (0.05–0.45) in our analyses. Input parameters, that is, mRS at 90 days, and the model structure may explain the difference between our results and previous results. mRS distributions at 90 days were obtained from meta-analyses of 6 RCTs in our

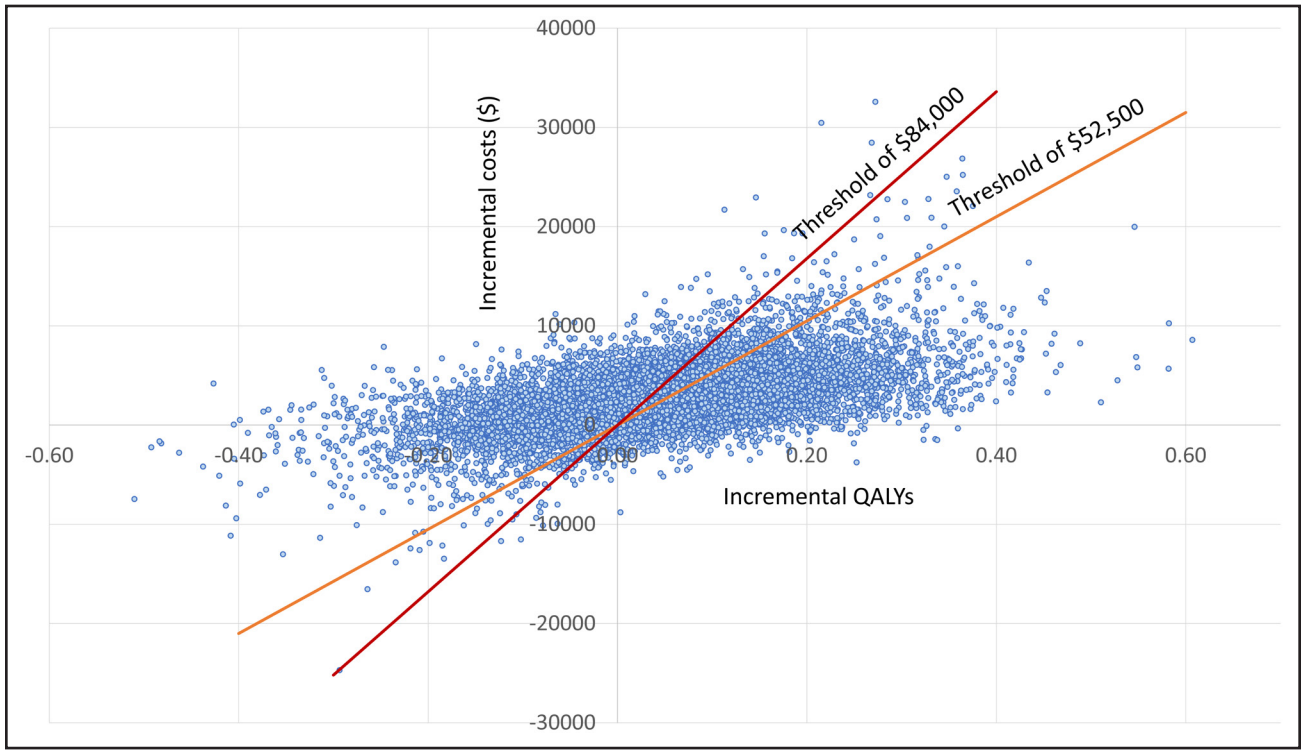

Figure 2. Incremental cost-effectiveness plane of intravenous alteplase before endovascular thrombectomy (EVT) vs EVT alone in base case.
QALY indicates quality-adjusted life year.

study, whereas Ospel et al[9] and Han et al[8] used data from DIRECT-MT, and Qureshi et al[28] applied data from 4 RCTs (DIRECT-MT, SKIP, DEVT, and MR CLEAN-NO IV). Also, previous studies[8,28] considered 3 health states in the model, including good outcome (mRS score of 0–2), poor outcome (mRS score of 3–5), and death (mRS score of 6). In contrast, we included 5 health states (mRS scores of 0–1, 2–3, 4, and 5 and death) based on mRS score 3 being more similar to mRS score 2 than to mRS score 4 in terms of health-related quality-of-life scores.[12] Recently, an economic evaluation[29] based on individual patient-level data from DIRECT-MT showed that EVT alone did not achieve (economic) dominance over intravenous alteplase before EVT for patients with LVO in China. In addition, a recent modeling study[30] revealed that intravenous alteplase before EVT had a probability of being cost-effective of 58% in Canada and 67% in China from a payer perspective.

The European Stroke Organisation recommends IVT before EVT over EVT alone for anterior circulation LVO patients admitted to EVT-capable centers within 4.5 hours from symptom onset, though IVT should not increase time delays for the initiation of EVT.[31] Although effectiveness of treatments remains a major factor in clinical practice, cost-effectiveness data may prioritize treatment given scarce health care resources in different settings. Our findings may be transferred to similar health care settings at different WTP thresholds. Given the lack of consistency in effectiveness of EVT alone versus IVT before EVT, our study highlights the relevance of further economic evaluation based on individual patient data from the 6 RCTs and the relevance of separate evaluations for different settings such as time from onset to treatment. Moreover, tenecteplase (a genetically modified form of tissue-type plasminogen activator) before EVT has been demonstrated a better mRS distribution at 90 days than alteplase before EVT in patients with LVO within 4.5 hours from symptom onset.[32,33] Economic analyses also revealed that tenecteplase was cost-effective compared with alteplase for patients with acute ischemic stroke before EVT.[10,34] This may imply that tenecteplase before EVT could add benefit and may also appear cost-effective.

Our study has several limitations. First, mRS distributions at 90 days were derived from the meta-analyses of published studies, limiting the possibility of specific subgroup analyses. Second, small numbers of follow-up patients in the MR CLEAN trial could affect the reliability of long-term extrapolation through the transition probabilities, which is why we were required to combine mRS scores of 0 to 1 and 2 to 3 in our model. Third, this study did not consider adverse event costs in the model due to the lack of cost data. Although symptomatic intracranial hemorrhage rates did not significantly differ between the 2 treatments, symptomatic intracranial hemorrhage rates in the EVT-alone group were slightly lower in the

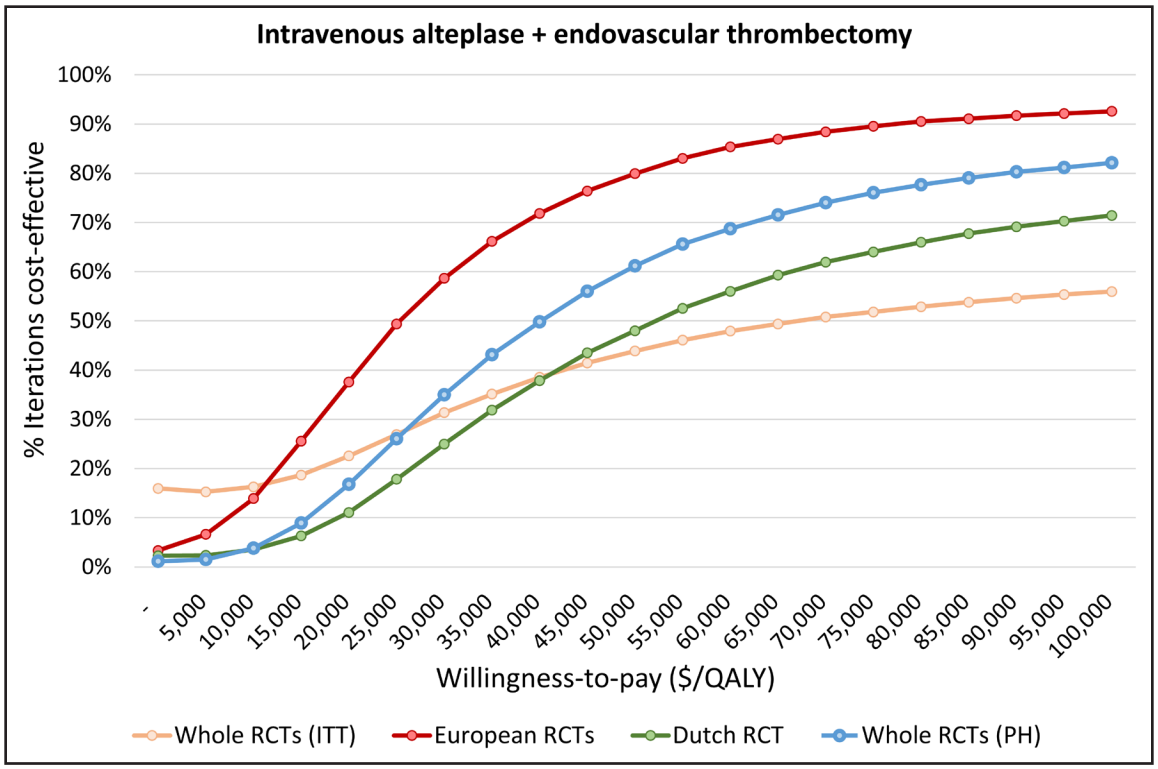

Figure 3. Cost-effectiveness acceptability curves of intravenous alteplase before endovascular thrombectomy.
ITT indicates intention to treat; PH, post hoc; QALY, quality-adjusted life year; and RCT, randomized controlled trial.

meta-analysis of 6 RCTs (4.3% in EVT alone versus 5.4% in alteplase before EVT),[7] possibly resulting in lower cost of symptomatic intracranial hemorrhage treatment. Further, we used annual costs during the first year instead of dividing into costs up to 90 days and costs from 90 days to 1 year due to the lack of data on time-specific costs. In addition, we only included direct medical costs in this study. Informal care needs to be considered, as previous studies have reported that 54% to 80%[35,36] of patients receive informal care of which the costs have been estimated to be €4320 ($4838)[37] per patient in the first 2 years after stroke. Finally, we considered IVT with alteplase in this cost-effectiveness study, as tenecteplase is not currently used for patients with LVO in the Netherlands (though the European Stroke Organisation recommends tenecteplase 0.25 mg/kg over alteplase 0.9 mg/kg for patients with LVO within 4.5 hours of symptom onset).[38] Future work should address whether tenecteplase before EVT is cost-effective compared with EVT alone and may identify specific patients with LVO receiving benefit of IVT, that is, early time window from onset to IVT.

In conclusion, intravenous alteplase before EVT might not be cost-effective compared with EVT alone for patients with LVO at the WTP threshold of $52 500 but has a higher probability of being cost-effective at the threshold of $84 000 in the Netherlands. The mRS distribution at 90 days derived from different populations had a high impact on the cost-effectiveness of intravenous alteplase before EVT. These findings suggest that intravenous alteplase before EVT may still provide economic benefit in eligible patients admitted to EVT-capable centers and that different settings play a pivotal role in value for money of intravenous alteplase before EVT.

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Supplemental Material

Tables S1–S6
Figures S1–S10
CHEERS Checklist

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