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Original research

# Costs and health effects of CT perfusion-based selection for endovascular thrombectomy within 6 hours of stroke onset: a model-based health economic evaluation

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## ABSTRACT

**Background** Although CT perfusion (CTP) is often incorporated in acute stroke workflows, it remains largely unclear what the associated costs and health implications are in the long run of CTP-based patient selection for endovascular treatment (EVT) in patients presenting within 6 hours after symptom onset with a large vessel occlusion.

**Methods** Patients with a large vessel occlusion were included from a Dutch nationwide cohort (n=703) if CTP imaging was performed before EVT within 6 hours after stroke onset. Simulated cost and health effects during 5 and 10 years follow-up were compared between CTP based patient selection for EVT and providing EVT to all patients. Outcome measures were the net monetary benefit at a willingness-to-pay of €80 000 per quality-adjusted life year, incremental cost-effectiveness ratio, difference in costs from a healthcare payer perspective ( $\Delta$ Costs) and quality-adjusted life years ( $\Delta$ QALY) per 1000 patients for 1000 model iterations as outcomes.

**Results** Compared with treating all patients, CTP-based selection for EVT at the optimised ischaemic core volume (ICV $\geq$ 110 mL) or core-penumbra mismatch ratio (MMR $\leq$ 1.4) thresholds resulted in losses of health (median  $\Delta$ QALYs for ICV $\geq$ 110 mL: –3.3 (IQR: –5.9 to –1.1), for MMR $\leq$ 1.4: 0.0 (IQR: –1.3 to 0.0)) with median  $\Delta$ Costs for ICV $\geq$ 110 mL of –€348 966 (IQR: –€712 406 to –€51 158) and for MMR $\leq$ 1.4 of €266 513 (IQR: €229 403 to €380 110)) per 1000 patients. Sensitivity analyses did not yield any scenarios for CTP-based selection of patients for EVT that were cost-effective for improving health, including patients aged  $\geq$ 80 years

**Conclusion** In EVT-eligible patients presenting within 6 hours after symptom onset, excluding patients based on CTP parameters was not cost-effective and could potentially harm patients.

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Although only recommended for selecting patients for endovascular treatment (EVT) after 6 hours from stroke onset, advanced brain imaging including CT perfusion is often incorporated into the workflow for patients suspected of acute ischaemic stroke. However, it remains largely unclear what the associated costs and health implications are in the long run of CT perfusion (CTP)-based patient selection for EVT in patients presenting within 6 hours after symptom onset. Furthermore, the effect of varying decision thresholds and treatment benefits of EVT remains poorly understood.

## WHAT THIS STUDY ADDS

⇒ Compared with treating all patients, CTP-based selection for EVT at the optimised ischaemic core volume (ICV $\geq$ 110 mL) or core-penumbra mismatch ratio (MMR $\leq$ 1.4) thresholds, resulted in a loss of health (median  $\Delta$ quality-adjusted life years for ICV $\geq$ 110 mL: –3.3 (IQR: –5.9 to –1.1), for MMR $\leq$ 1.4: 0.0 (IQR: –1.3 to 0.0)) with median  $\Delta$ Costs for ICV $\geq$ 110 mL of –€348 966 (IQR: –€712 406 to –€51 158) and for MMR $\leq$ 1.4 of €266 513 (IQR: €229 403 to €380 110)) per 1000 patients. Sensitivity analyses did not yield any scenarios for CTP-based selection of patients for EVT that were cost-effective for improving health, including for patients aged above 80 years.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Selecting patients for EVT within 6 hours of ischaemic stroke onset using CTP will likely result in a loss of health and at best minor cost savings.

## INTRODUCTION

Penumbra and ischaemic core volume (ICV) measured with CT perfusion (CTP) are used to identify salvageable and non-salvageable brain tissue in patients with acute ischaemic stroke (AIS).<sup>1</sup> Moreover, patients with a large penumbra are suggested to benefit more from revascularisation therapies such as endovascular treatment (EVT) while patients with a large ICV are more likely to have poor outcomes irrespective of treatment.<sup>1</sup> If CTP could be used to identify patients where EVT is futile, EVT costs might be saved. However, inaccuracies in predicting futile EVT might exclude patients from beneficial treatment and could therefore cause harm. Health economic model-based analyses can be used to estimate long-term costs and health effects for various scenarios and uses of CTP for EVT patient selection.

Three recent randomised clinical trials (RCTs) in patients with large infarct regions assessed with plain CT or CTP concluded that EVT results in more favourable functional outcomes compared with best medical management.<sup>2–4</sup> Similarly, a pooled analysis of the initial seven landmark EVT trials showed a benefit of EVT in patients with large ischaemic lesions on non-contrast enhanced CT.<sup>5</sup> Although the RCT that selected patients using CTP-based ICV and core-penumbra mismatch ratio (MMR) had a higher EVT benefit than the other RCTs,<sup>6</sup> no statistically significant decay of EVT effect related to these CTP measures was observed in a pooled analysis of five landmark EVT trials.<sup>1</sup> Additional post hoc analyses identified a reduction in EVT benefit depending on ICV in patients aged  $\geq 75$  years.<sup>7</sup> As a result, discrepancies exist between European and North American guidelines and CTP is still frequently considered to guide patient selection for EVT.<sup>8–10</sup> Since recent large stroke trials had restrictive inclusion criteria, varying imaging protocols, and only evaluated patient outcome at 90 days follow-up,<sup>2–4</sup> it remains partially unclear what the long-term costs and health effects are of selecting patients for EVT based on CTP measures.

Three previous model-based studies had conflicting results regarding the cost-effectiveness of CTP for patients presenting within 6 hours.<sup>11–13</sup> These three studies were based on fixed assumptions for the EVT effect, EVT effect modification due to CTP measures and fixed decision threshold based on CTP measures. As a result, these studies do not consider population variations and uncertainty in current evidence.<sup>1–6</sup> Namely, the EVT effect could be lower in patients with a large infarct or in elderly subgroups.<sup>7</sup> In addition, the optimal ICV or MMR thresholds for EVT selection remain a matter of debate. Furthermore, due to improvements in CTP acquisition and analytical software, previous evidence for ICV and MMR-based EVT effect modification and associations with functional outcome might be inaccurate.<sup>14</sup> Finally, costs and health effect estimates from previous studies were adapted from a US perspective which might not apply to European and other healthcare systems.<sup>11–13</sup>

We aimed to quantify the long-term costs and health effects of CTP-estimated ICV and MMR to select patients within 6 hours after stroke onset for EVT in the Netherlands compared with providing EVT to all patients. Furthermore, we aimed to identify scenarios where CTP-based patient selection for EVT might be cost-effective.

## METHODS

### Study design

The cost-effectiveness of CTP for patients with acute ischaemic stroke (CLEOPATRA) is a Dutch nationwide, retrospective, multicentre health economic modelling study using patient-level data and literature parameters.<sup>15</sup> A cohort of patients with a large

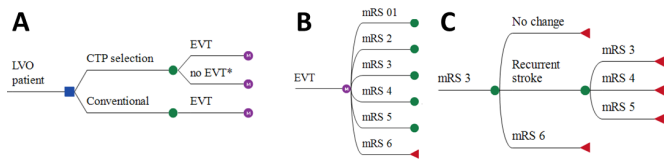
vessel occlusion (LVO) that received EVT after CTP imaging with 90-day functional outcome according to the modified Rankin Scale (mRS) was considered. During inclusion, the standard of care was to provide EVT to all patients regardless of the CTP measures.<sup>8</sup> We compared CTP-based patient selection for EVT ('CTP select EVT' arm) with providing EVT to all patients ('all EVT' arm). The decision to offer or withhold EVT in the CTP arm was dependent on optimised ICV or MMR thresholds per patient. Since we used observational data of patients who underwent EVT, available ORs for treatment effect,<sup>6, 16</sup> and treatment effect modification due to CTP measures<sup>1</sup> were used to generate the 90-day mRS as if those patients did not undergo EVT (referred to as the 'no EVT group'). We assumed that EVT could directly follow after imaging and that CTP would not delay time to EVT. The methodology for the no EVT group generation is described in online supplemental A. Our models' input parameters were chosen to represent scenarios that are more favourable for CTP-based EVT patient selection so we can argue what the best achievable returns in terms of costs and health might be.

### Data collection

Patients who had CTP before EVT in an EVT-capable stroke centre for an anterior circulation LVO between January 2018 and March 2022 were included from the following data sources: the Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in The Netherlands (MR CLEAN)-NO IV (ISRCTN80619088),<sup>17</sup> MR CLEAN-MED (ISRCTN76741621),<sup>18</sup> the MR CLEAN Registry,<sup>19</sup> and a local cohort of patients from our comprehensive stroke centre. A detailed overview of the study-specific inclusion and exclusion criteria were previously published together with predefined modelling procedures and study endpoints.<sup>15</sup> Online supplemental B describes minor changes to the protocol.<sup>15</sup> CTP acquisition, post-processing and quality assessment are presented in detail in online supplemental C.<sup>15</sup> In short, perfusion analysis was centrally performed by a trained observer using syngo.via CT Neuro Perfusion (V.VB40, Siemens Healthcare, Forchheim, Germany). The ICV was estimated using a threshold cerebral blood volume (CBV)  $< 1.2$  mL/100 mL and the critically hypoperfused tissue (including penumbra) was defined as CBF  $< 27$  mL/100 mL/min. For patients included in the MR CLEAN-MED and MR CLEAN-NO IV trials, deferred consent was received, for patients included in the MR CLEAN Registry and the retrospective local cohort a waiver for informed consent was provided by the institutional review board. Data is available on reasonable request and following local privacy regulations.

### Modelling approach

A Markov model with patient-level micro-simulations was used to simulate 5-year and 10-year follow-up. These follow-up terms were based on previous research where validation of the proposed simulation model was accurate at 5 years and at 10 years the majority of the simulated population had died.<sup>20</sup> Furthermore, life-time simulations would have led to unrealistic survival rates of this predominantly elderly and comorbid population. The model consisted of a short-term 90-day post-AIS model to simulate EVT patient selection strategies followed by a long-term yearly model (figure 1) and was used to simulate functional outcome measured with the mRS. In the long-term model, deterioration of mRS was simulated based on the probability of stroke recurrence<sup>21</sup> and death<sup>22</sup> inflated with patient-specific HRs.<sup>23</sup> Simulations and analyses were performed with publicly available custom-developed Python software (github.



**Figure 1** Markov model structure. (A) Patients with a confirmed large vessel occlusion (LVO) who were eligible for endovascular treatment (EVT) were simulated. Each patient was simulated as if NCCT and CTA imaging was used with or without additional CT perfusion (CTP) for selection of patients for EVT. In the CTP arm, the decision for EVT was based on varying thresholds for ischaemic core volume and core-penumbra mismatch ratio. In the conventional arm, all patients underwent EVT. (B) After EVT or no EVT the 90-day modified Rankin Scale (mRS) was modelled based on observed mRS (EVT group) or adjusted mRS with ORs (no EVT group). (C) After the 90-day outcome, yearly mRS transitions were modelled based on death and recurrent stroke rates. \*:The proportion of patients that do not receive EVT differs based on the set ischaemic core volume or core-penumbra mismatch ratio thresholds. non-contrast CT (NCCT);CT angiography (CTA).

com/henkvanvoorst92/CLEOPATRA). All model input parameters are described in online supplemental D.

### Costs and quality-adjusted life years

Costs in euros (€) from a healthcare payer perspective and quality-adjusted life years (QALYs) over the simulated period were derived per mRS subscore in a previous study<sup>20</sup> and predefined in our protocol.<sup>15</sup> Online supplemental D provides an overview of all model input parameters. Acute care costs included personnel cost, radiological imaging, EVT procedure and thrombolysis costs. Long-term follow-up costs considered in-hospital care use, outpatient clinical visits, rehabilitation, formal homecare and long-term institutionalised care. Present values of simulated costs and QALYs were calculated based on a discounting rate of 4% for QALYs and 1.5% for costs yearly.<sup>24</sup> Historical and forecasted inflation rates for healthcare costs were used to adjust the costs over time.<sup>25 26</sup>

### Outcome measures

The primary outcome was the net monetary benefit (NMB: Formula 1) at a willingness-to-pay of €80 000 per QALY of CTP-based EVT patient selection (CTP) compared with the conventional imaging arm (no CTP). Secondary outcome measures were the incremental cost-effectiveness ratio (ICER: Formula 2), and differences in cost ( $\Delta$ Costs) and  $\Delta$ QALYs between the simulated CTP and no CTP arms.

$$NMB = [WTP \times (QALY_{CTP \text{ select EVT}} - QALY_{all EVT})] - (Costs_{CTP \text{ select EVT}} - Costs_{all EVT}) \quad (1)$$

$$ICER = \frac{(Costs_{CTP \text{ select EVT}} - Costs_{all EVT})}{(QALY_{CTP \text{ select EVT}} - QALY_{all EVT})} \times 1000 \text{ patients} \quad (2)$$

### Baseline and sensitivity analyses

Mean values of the model inputs were used for the baseline simulation including all patients once. Baseline simulation EVT patient exclusion thresholds were  $\geq 70$  mL for ICV and  $\leq 1.8$  for MMR. In the one-way sensitivity analyses, the effect on outcomes of a 10% increase or decrease of input parameters relative to the baseline simulation was simulated. In the probabilistic sensitivity analyses (PSAs), 1000 cohorts of 703 patients were sampled with replacement from the original data. Each cohort contains a proportion of patients that did not receive EVT in

the CTP arm since they had an ICV above or MMR below the decision threshold. ICV and MMR values were varied with increments of 10 between 0 and 150 mL and increments of 0.2 between 1.4 and 2.4, respectively. The decision threshold with the highest median NMB across all cohorts was chosen as the optimal setting. Per simulated cohort, the  $\Delta$ Costs and  $\Delta$ QALYs between the CTP and no CTP arms were computed. All PSA results were reported as the median with IQR over the 1000 simulated cohort per 1000 patients.

A baseline PSA was conducted using an OR for the EVT effect from the MR CLEAN trial (OR: 1.67 (95% CI: 1.21 to 2.30)).<sup>16</sup> We performed dedicated PSAs altering the OR and 95% CI for EVT effect with  $-0.5$  to  $-0.3$ ,  $+0.3$  and  $+0.82$ . The lower bound ( $-0.5$ ) corresponds approximately to the EVT effect in patients with a large infarct in non-contrast CT (NCCT) (Alberta Stroke Program Early CT score  $\leq 5$ ) and the upper bound ( $+0.82$ ) refers to the pooled EVT effect in the Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials (HERMES) meta-analysis.<sup>6</sup> The regression analyses for EVT effect modification due to CTP estimated ICV and MMR by Campbell *et al* were repeated as the initial work only reported p values (full analyses in online supplemental D).<sup>1</sup> An OR for EVT effect modification due to ICV (OR: 0.98 (95% CI: 0.881 to 1.091) per 10 mL) and MMR (OR: 1.010 (95% CI: 0.994 to 1.026)) per one point change) were used for baseline simulations. Since these ORs were based on CTPs from trials published between 2015 and 2017 with limited brain coverage,<sup>1 27</sup> the ORs and 95% CIs for effect modification were altered by  $-0.1$  and  $-0.05$  for ICV, and  $+0.1$  and  $+0.05$  for MMR to consider technological improvements in CTP software. Finally, we simulated the most favourable CTP-based EVT patient selection PSA scenario considering patients aged  $\geq 80$  years, a 0.3 decrease of the EVT effect OR (OR: 1.37 (95% CI: 0.91 to 2.0)), and a 0.1 decrease of the ICV or MMR based EVT effect modification (OR: 0.88 (95% CI: 0.781 to 0.991)) for 10 years of follow-up.

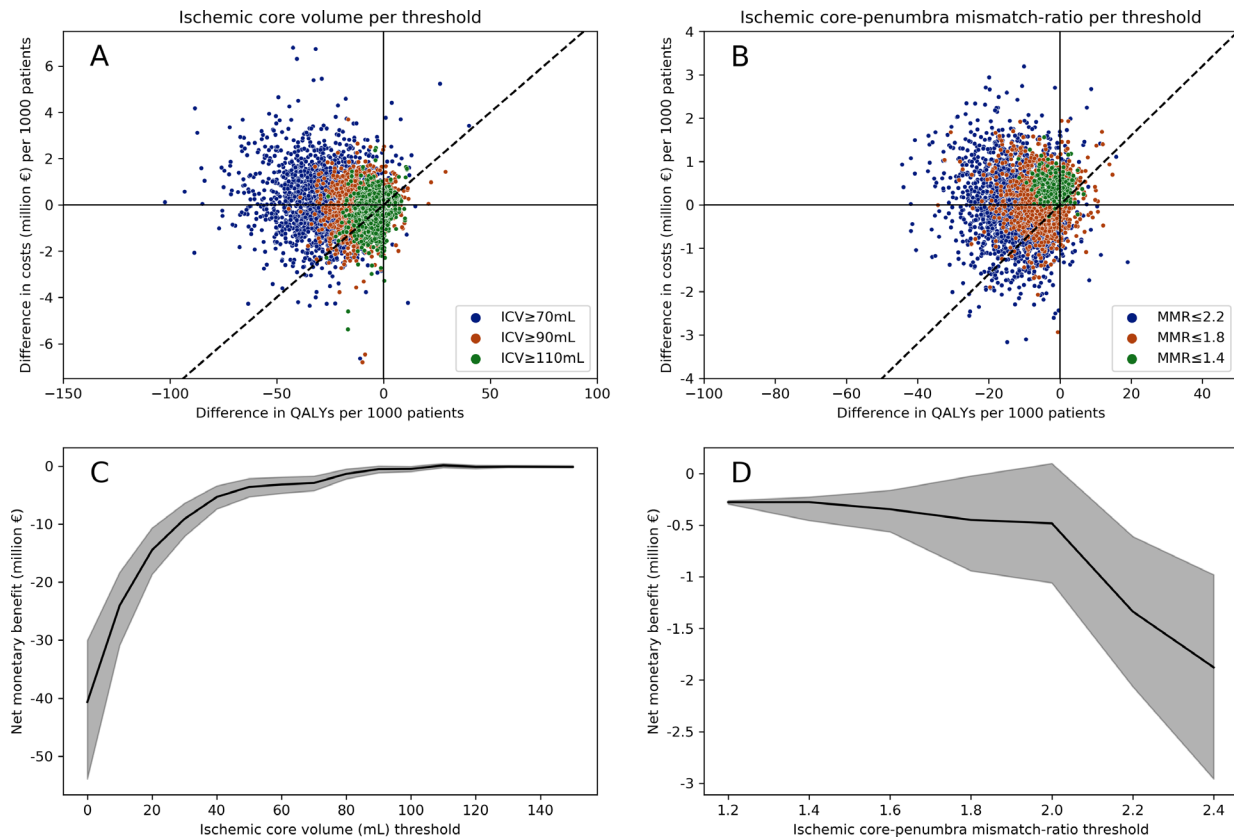
## RESULTS

### Descriptive statistics

A total of 703/1122 patients from the CLEOPATRA database were considered in this study (MR CLEAN NO IV  $n=228$ , MR CLEAN MED  $n=118$ , MR CLEAN Registry  $n=275$ , local cohort  $n=82$ ). Online supplemental E contains the exclusion reasons (online supplemental figure E1) and tables with baseline characteristics (online supplemental tables E1–3). The main exclusion reasons were: presentation beyond 6 hours after symptom onset and CTP source data that could not be processed due to anonymisation at local sites or discrepancies between local hardware and our CTP software. There were 70/703 (10.0%) patients with an  $ICV \geq 70$  mL, 23/703 (3.3%) patients with an  $ICV \geq 110$  mL, 19/703 (2.7%) patients with an  $MMR \leq 1.8$  and 5/703 (0.7%) patients with an  $MMR \leq 1.4$ .

### Baseline model and one-way sensitivity

In the baseline simulations, excluding patients with an  $ICV \geq 70$  mL for EVT resulted in losses of health ( $\Delta$ QALY:  $-33.8$ ), higher costs ( $\Delta$ costs: €385 866), an ICER of  $-11 432$  and NMB of  $-\text{€}3 086 208$  per 1000 patients. Excluding patients with an  $MMR \leq 1.8$  for EVT resulted in losses of health ( $\Delta$ QALY:  $-5.8$ ), higher costs ( $\Delta$ costs: €54 836), an ICER of  $-9834$  and NMB of  $-\text{€}500 913$  per 1000 patients. Online supplemental figure F1 describes the 10 model parameters that affected the NMB the most in strategies using ICV or MMR for EVT patient selection. For the ICV simulations, the QALYs for mRS 0–2,



**Figure 2** Probabilistic sensitivity analyses results. (4A–B) Each point in the scatter plot is a cohort of patients that was simulated twice; one time as if the optimal CTP measure (CTP arm) was used to exclude patients for EVT and one time as if all patients received EVT (no CTP arm). The x and y coordinates of this cohort are based on the differences in QALYs and costs between these two simulated arms and thus represent the benefit or harm due to CTP-based patient selection. The dashed diagonal line represents the willingness-to-pay of €80 000 per QALY; below the line is cost-effective. The colours were used to show the effect of different ICV and MMR decision thresholds for patient exclusion for EVT. (4C–D) The trend observed in 4A–B for different decision thresholds is presented per 10 mL ICV and 0.2 MMR decision threshold increments on the x-axis with a net monetary benefit on the y-axis. The black line represents the median, the grey area the IQR. The net monetary benefit aggregates the QALY and cost differences between the CTP and no CTP arms to a single value by multiplying the QALY difference with €80 000 and subtracting the cost difference. (4A) Incremental cost-effectiveness ratio plot for varying ICV thresholds for EVT patient selection. (4B) Incremental cost-effectiveness ratio plot for varying MMR thresholds for EVT patient selection. (4C) The net monetary benefit for each 10 mL increment of the ICV threshold, the optimal threshold was  $\geq 110$  mL. (4D) Similar to 4C but considers the MMR, the optimal threshold was  $\leq 1.4$ . CTP, CT perfusion; EVT, endovascular treatment; ICV, ischaemic core volume; MMR, core-penumbra mismatch ratio; QALYs quality-adjusted life-years.

long-term costs in the third year and beyond for mRS 5 and costs of EVT affected NMB the most. For the MMR simulations, the QALYs in mRS 3–4, costs of EVT and the costs related to mRS 4 in the first year after AIS affected NMB the most.

### Probabilistic sensitivity analysis

Figure 2 depicts the PSA results in ICER plots (figure 2), and the NMB per decision threshold for ICV and MMR-based patient selection (figure 2). A more detailed overview of the results is provided in online supplemental F. For all PSAs the optimal thresholds for EVT patient exclusion using were  $\text{ICV} \geq 110$  mL and  $\text{MMR} \leq 1.4$ . Using  $\text{ICV} \geq 110$  mL to exclude patients for EVT resulted in losses of health ( $\Delta\text{QALYs}$  5-year median:  $-3.3$  (IQR:  $-5.9$  to  $-1.1$ ), 10-year median:  $-4.3$  (IQR:  $-9.1$  to  $-0.7$ )), limited cost savings ( $\Delta\text{Costs}$  5-year median:  $-\text{€}348\,966$  (IQR:  $-\text{€}712\,406$  to  $-\text{€}51\,158$ ), 10-year median:  $-\text{€}246\,679$  (IQR:  $-\text{€}733\,714$  to  $\text{€}191\,840$ )), wide IQRs for the ICER (ICER 5-year median:  $71\,346$  (IQR:  $-16\,517$  to  $181\,241$ ), 10-year median:  $31\,244$  (IQR:  $-48\,780$  to  $141\,749$ )) and NMBs bracketing zero (NMB 5-year median:  $\text{€}102\,227$  (IQR:  $-\text{€}282\,942$  to  $\text{€}431\,923$ ), 10-year median:  $-\text{€}97\,781$

(IQR:  $-\text{€}644\,889$  to  $\text{€}420\,136$ )) per 1000 patients. Using  $\text{MMR} \leq 1.4$  to exclude patients for EVT resulted in limited to no losses of health ( $\Delta\text{QALYs}$  5-year follow-up median:  $0.0$  (IQR:  $-1.3$  to  $-0.0$ ), 10-year follow-up median:  $0.0$  (IQR:  $-1.6$  to  $-0.0$ )), higher costs ( $\Delta\text{Costs}$  5-year follow-up median:  $\text{€}266\,513$  (IQR:  $\text{€}229\,403$  to  $\text{€}380\,110$ ), 10-year follow-up median:  $\text{€}279\,661$  (IQR:  $\text{€}229\,403$  to  $\text{€}464\,756$ )), high ICERs with wide IQRs (ICER 5-year follow-up median:  $312\,955$  (IQR:  $-141\,379$  to infinite), 10-year follow-up median:  $249\,523$  (IQR:  $-118325$  to infinite)) and negative NMBs (NMB 5-year follow-up median:  $-\text{€}278\,626$  (IQR:  $-\text{€}456\,559$  to  $-\text{€}229\,403$ ), 10-year follow-up median:  $-\text{€}279\,614$  (IQR:  $-\text{€}555\,168$  to  $-\text{€}228\,836$ )) per 1000 patients. Due to the limited number of patients with an ICV above ( $\geq 110$  mL) and MMR below ( $\leq 1.4$ ) the optimal decision threshold for EVT patient exclusion, the  $\Delta\text{QALY}$  results were low. This effect was more profound for MMR compared with ICV-based patient selection; low MMR values were less common than high ICV values. The effect on costs in this small group of patients excluded for EVT was due to a decrease in long-term care costs, related to earlier death and due to the absence of EVT

**Table 1** NMB for alternative scenarios of EVT effect and effect modification due to ICV and MMR per 1000 patients

CTP measure and optimised threshold	Follow-up horizon (years)	Effect modification due to ICV or MMR (OR)	Net monetary benefit (NMB) in € per 1000 patients						2.49 (95% CI: 2.03 to 3.12)†
			1.17 (95% CI: 0.71 to 1.8)†	1.37 (95% CI: 0.91 to 2.0)	1.67 (95% CI: 1.21 to 2.3)*	1.97 (95% CI: 1.51 to 2.6)	EVT effect OR		
ICV ≥ 110 mL	5	0.98 (95% CI: 0.881 to 1.091)*	75260 (-256 606 to 356 220)	92540 (-274 492 to 387 168)	102227 (-282 942 to 431 923)	115014 (-282 947 to 472 304)	126436 (-294 179 to 516 591)		
	5	0.93 (95% CI: 0.831 to 1.041)	52532 (-158 294 to 247 178)	58740 (-171 751 to 270 871)	71360 (-189 586 to 298 635)	81540 (-202 099 to 334 318)	95139 (-235 410 to 378 627)		
	5	0.88 (95% CI: 0.781 to 0.991)	44361 (-84 207 to 180 651)	45137 (-97 373 to 189 920)	52380 (-117 014 to 211 993)	57805 (-103 484 to 233 197)	69596 (-146 628 to 265 746)		
	10	0.98 (95% CI: 0.881 to 1.091)*	-119 896 (-587 168 to 333 612)	-112 504 (-620 679 to 366 957)	-97 781 (-644 889 to 420 136)	-103 484 (-659 676 to 460 891)	-74 712 (-685 404 to 519 196)		
	10	0.93 (95% CI: 0.831 to 1.041)	-82 733 (-430 820 to 215 513)	-89 848 (-460 125 to 247 493)	-95 305 (-508 231 to 268 169)	-94 125 (-521 341 to 297 295)	-96 801 (-565 620 to 347 538)		
	10	0.88 (95% CI: 0.781 to 0.991)	-24 078 (-262 408 to 153 870)	-38 411 (-295 091 to 163 770)	-47 193 (-327 253 to 184 168)	-56 497 (-369 169 to 205 562)	-69 079 (-415 466 to 234 382)		
	MMR ≤ 1.4	5	1.010 (95% CI: 0.994 to 1.560)	-263 889 (141)	-267 393 (-443 666 to -225 803)	-278 626 (-456 559 to -229 403)	-279 614 (-465 361 to -229 379)	-279 614 (-477 472 to -229 403)	
		5	1.060 (95% CI: 1.044 to 1.610)	-264 070 (-433 655 to -222 185)	-267 548 (-444 090 to -225 943)	-278 740 (-456 835 to -229 403)	-279 614 (-465 472 to -229 360)	-279 614 (-477 681 to -229 403)	
		5	1.110 (95% CI: 1.094 to 1.660)	-264 073 (227)	-267 696 (-444 428 to -226 076)	-278 850 (-457 097 to -229 403)	-279 614 (-465 577 to -229 342)	-279 614 (-477 880 to -229 403)	
		10	1.010 (95% CI: 0.994 to 1.560)	-271 910 (-520 757 to -219 184)	-279 614 (-534 853 to -222 380)	-279 614 (-555 168 to -228 836)	-279 614 (-570 464 to -229 403)	-279 614 (-589 096 to -229 403)	
10	1.060 (95% CI: 1.044 to 1.610)	-272 133 (-521 893 to -219 316)	-279 614 (-535 771 to -222 362)	-279 614 (-555 982 to -228 996)	-279 614 (-571 036 to -229 403)	-279 614 (-589 859 to -229 403)			
	1.110 (95% CI: 1.094 to 1.660)	-272 027 (-521 338 to -219 251)	-279 614 (-535 334 to -222 371)	-279 614 (-555 585 to -228 917)	-279 614 (-570 770 to -229 403)	-279 614 (-589 487 to -229 403)			

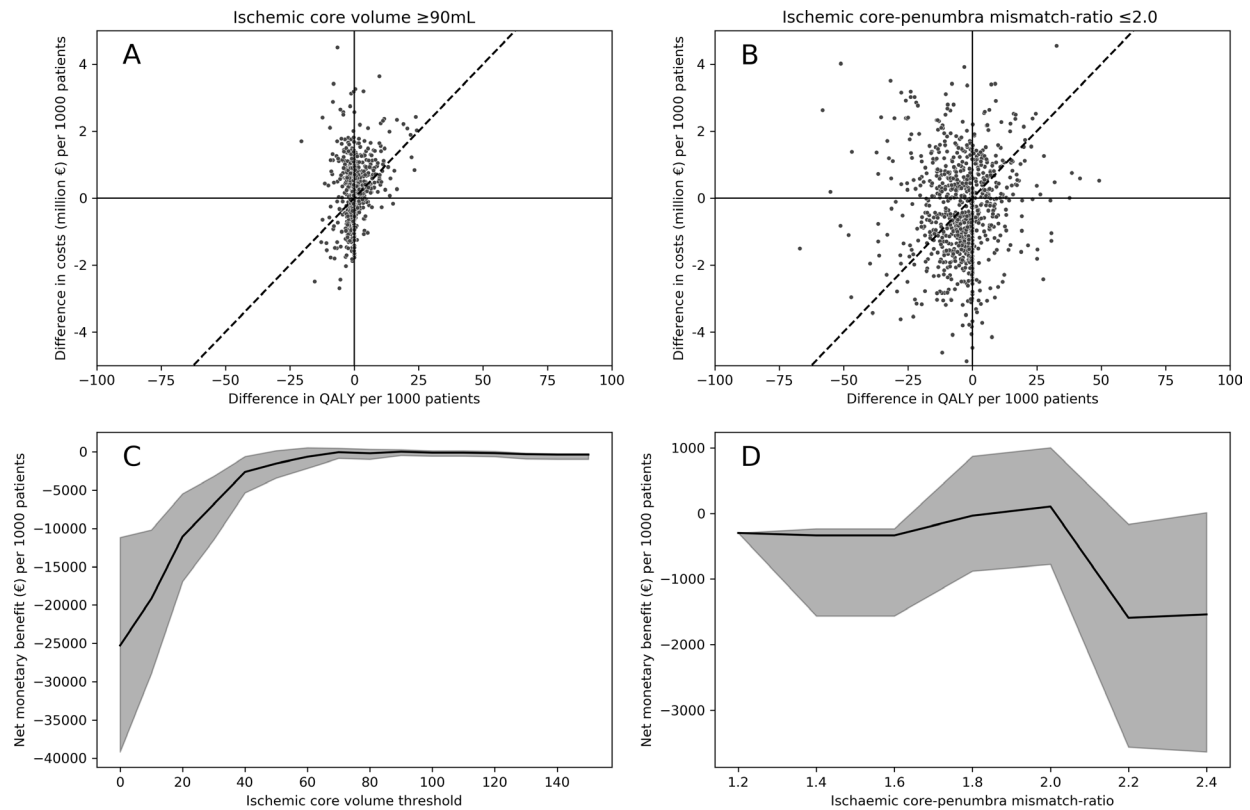
Results are presented as median with IQR, the baseline follow-up horizon of 5-year was used. The optimal ICV threshold for patient exclusion for EVT was in all scenarios ≥ 110 mL, the optimal MMR threshold for patient exclusion for EVT was ≤ 1.4 in all scenarios. Optimal thresholds were based on the maximum net monetary benefit at a willingness-to-pay of €80 000.

\* The baseline ORs from the MR CLEAN trial for EVT effect<sup>3</sup> and the study by Campbell *et al* for ICV-based effect modification.<sup>4</sup>

† Just below the mean EVT effect of patients with a large infarct on NCCT (Alberta Stroke Program Early CT < 6) in the HERMES pooling.

‡ EVT effect found in the HERMES pooling.<sup>1</sup> A lower EVT effect and a lower ICV or MMR-based EVT effect modification are more beneficial scenarios for using CTP for EVT patient selection.

CTP, CT perfusion; EVT, endovascular treatment; ICER, incremental cost effectiveness ratio; ICV, ischaemic core volume; MMR, core-penumbra mismatch ratio.



**Figure 3** ICER plot for CTP-based EVT selection in an elderly population. For this simulation a follow-up horizon of 10 years, 0.3 decrease of the EVT effect (OR: 1.37 (95% CI: 0.91 to 2.0)), and a 0.1 decrease of the ICV or MMR based EVT effect modification (OR: 0.88 (95% CI: 0.781 to 0.991)) were used to simulate cohorts with patients aged  $\geq 80$  years. This is a favourable but unlikely scenario for CTP-based selection for EVT. (5A) PSA performed for ICV with an optimal threshold of  $\geq 90$  mL for excluding patients for EVT. (5B) PSA performed for MMR with an optimal threshold of  $\leq 2.0$  for excluding patients for EVT. (5C–D) Per ischaemic core volume and mismatch-ratio threshold the NMB for the most favourable scenario for CTP-based EVT patient selection. EVT, endovascular treatment; ICV, ischaemic core volume; MMR, core-penumbra mismatch ratio; PSA, probabilistic sensitivity analysis.

costs. Subsequently, low  $\Delta$ QALY values resulted in ICERs with a wide IQRs.

### Changes in EVT effect and ICV or MMR-based effect modification

Table 1 describes the ICERs for different shifted values for the EVT effect and EVT effect modification due to ICV or MMR from the baseline levels. Online supplemental F, G, and H contain more scenarios and reports the ICER,  $\Delta$ Costs and  $\Delta$ QALYs. For the simulations using ICV, a higher EVT effect resulted in a higher cost saving, a higher QALY loss and a higher ICER and NMB. A decrease in the ICV-based EVT effect modification resulted in lower cost savings, less losses of health, lower NMBs coinciding with narrower IQRs. For the simulations using MMR, changes in EVT effect or the MMR-based EVT effect modification had a negligible effect on the outcome measures. This was mainly due to the small proportion of patients that had an  $\text{MMR} \leq 1.4$ . Even at the lowest EVT effect and ICV or MMR-based EVT effect modification (lower left corner in the table), the IQR of ICER and NMB included zero indicating no benefit of the use of CTP-based patient selection.

### Elderly subgroup: most favourable CTP for EVT selection scenario

Compared with similar model parameters (EVT effect OR: 1.37 (95% CI: 0.91 to 2.0), OR EVT\*ICV or MMR effect modification +0.1) and 10-year follow-up in the general population, the reduced life expectancy in the subgroup of patients  $\geq 80$

years resulted in a less profound losses of QALYs ( $\Delta$ QALYs ICV median: 0.0 (IQR:  $-0.8$  to  $0.5$ ), MMR median:  $-1.2$  (IQR:  $-8.8$  to  $0.0$ )) and additional costs ( $\Delta$ Costs ICV median: €34 920 (IQR:  $-\text{€}293\ 371$  to  $\text{€}524\ 269$ ), MMR median:  $-\text{€}229\ 448$  (IQR:  $-\text{€}1\ 178\ 568$  to  $\text{€}461\ 962$ )). However, IQRs of the ICER (ICV median: 120 757 (IQR:  $-343\ 877$  to  $932\ 702$ ), MMR median: 88 483 (IQR:  $61\ 501$  to  $653\ 609$ )) and NMB (ICV median: €23 425 (IQR:  $-\text{€}461\ 957$  to  $\text{€}305\ 633$ ), MMR median: €108 270 (IQR:  $-\text{€}775\ 446$  to  $\text{€}1\ 004\ 928$ )) per 1000 patients included zero. These results achieved optimal NMBs for an  $\text{ICV} \geq 90$  mL and  $\text{MMR} \leq 2.0$ . Figure 3 contains the ICER plot for the elderly subgroup PSA with the most favourable scenario for ICV and MMR-based patient selection.

### DISCUSSION

Even under unlikely favourable conditions, in patients aged  $\geq 80$  years, assuming a low EVT benefit, and a high decline of EVT effect due to ICV or MMR, CTP-based EVT patient selection was not cost-effective. In the baseline scenario, using the baseline CTP parameter estimates ICV or MMR for EVT patient selection within 6 hours after symptom onset resulted in no additional costs or cost savings and losses of health. Although positive median ICER and NMB estimates in the PSA would indicate a trend towards cost-effectiveness, the large uncertainty of these outcomes is represented by wide IQRs including negative values. Furthermore, the resulting positive ICER and NMB results originate from losses in health that coincide with cost savings. In

the short run, during 5-year follow-up, cost savings might be realised at the cost of losses of health. When considering longer 10-year follow-up horizons the cost savings declines while health losses increase, reducing the ICERs and NMBs. We observed a reduction in the loss of health and a reduction in cost savings for a lower EVT benefit and ICV-based EVT effect modification levels. For a low EVT effect and high reduction of EVT effect modification due to ICV and MMR, the simulation resulted—at best—in a negligible loss of health for no additional costs and thus an NMB close to zero.

To interpret the results of this study, the presented scenarios should be compared with the best available evidence. The EVT effect and EVT effect modification due to ICV and MMR were comparable to the effects found in two recent trials.<sup>2,3</sup> Therefore, the results from this study at baseline simulation values might present a scenario less favourable for outcomes after EVT and thus more favourable for CTP-based patient selection. In light of recent and ongoing AIS workflow improvements, it seems likely that the benefit of EVT will only increase in the coming years.<sup>28</sup> Since we did not observe a benefit of CTP-based patient selection in more favourable scenarios, technological improvements of CTP acquisition and software analyses might be futile to further improve CTP-based EVT patient selection.<sup>1</sup> Finally, in the most favourable CTP-based EVT patient selection scenario, we considered a lower EVT effect for patients aged  $\geq 80$  years. However, current evidence suggests a higher EVT effect for patients aged  $\geq 85$  years while we used a reduced EVT effect.<sup>29</sup> Other research suggests that patients aged  $\geq 75$  years with ICV  $\geq 50$  or  $\geq 85$  mL might have a lower EVT effect.<sup>7</sup>

Our study has limitations. First, we did not use prospectively collected data regarding treatment effect and CTP-based effect modification, long-term mRS follow-up, and cost data. Due to the retrospective nature of this study, we could have missed patients that would not benefit from EVT such as patients with a worse premorbid functional status. Second, we used cost data from a healthcare payer perspective, neglecting potential effects due to indirect costs related to, for example, labour productivity in young patients with AIS. Third, CTP might be used to improve occlusion detection and IVT administration.<sup>6,30</sup> Thus, the actual added value of CTP in the diagnostic workup of patients with AIS might be higher due to the beneficial effect on occlusion detection. Fourth, we only included CTP results from one single vendor with fixed settings. This reduces part of the variation in measurements compared with real-world measurements which likely vary between centres due to the variation of analytical CTP software packages.<sup>31,32</sup> As a result—even though no benefit of CTP for patient selection for EVT was found—findings from this study may be too optimistic, making it very unlikely that using CTP for the selection for EVT within 6 hours after symptom onset is currently—or, with improvements, will soon become—cost-effective. Further improvements in the CTP acquisition and analysis could also alter the association between the CTP measures and outcome, without EVT effect modification and thus affect the cost-effectiveness. This effect is not covered in this study.

Future work should investigate the cost-effectiveness of CTP-based patient selection in subpopulations with a high risk of poor functional outcome. For example, patients presenting after 6 hours from stroke onset, elderly patients,

patients with premorbid disability, or complex comorbidities as these patients might have a reduced benefit from EVT.<sup>33</sup> However, as represented by the baseline characteristics in this study, this combination of highly unfavourable baseline characteristics is rare in our AIS population.<sup>7</sup> Furthermore, long-term follow-up studies and cost-effectiveness analyses of the large infarct RCTs will provide a higher level of evidence.<sup>2-4</sup>

## CONCLUSION

In this Dutch nationwide cohort study with model-based health economics evaluation considering patients with large vessel occlusions presenting within 6 hours after symptom onset, CTP-based ischaemic core or core-penumbra MMR was not cost-effective for selecting patients for EVT. Although CTP-based selection might result cost-savings for minor losses of health in the short run, during 10 years of follow-up these cost-savings become negligible compared with the losses of health. Additional simulations revealed that under unlikely favourable conditions, these findings did not change.

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**Data availability statement** Data are available upon reasonable request. The complete de-identified patient data sets from the MR CLEAN-NO IV, and MR CLEAN-MED trials will be available from 18 months after publication until 15 years from publication. Data can be obtained from <https://www.contrast-consortium>.

nl/data-request-form/. The data will be made available to researchers who are CONTRAST consortium members or collaborators, and whose proposed use of the data has been approved by the CONTRAST data access and writing committee. The data will be made available for specified purposes, as defined in the substudy proposal and approved by the CONTRAST data access and writing committee. The data will be made available after approval of the proposal by the CONTRAST data access and writing committee. To ensure publication transparency and quality, researchers should adhere to the CONTRAST publication policy, accessible on <https://www.contrast-consortium.nl/publication-policy-contrast/>. For the patients included in the MR CLEAN Registry and the local cohort, individual patient data cannot be made available under Dutch law since we did not obtain patient approval for sharing individual patient data. All syntax files and output of statistical analyses are available on reasonable request to the corresponding author.

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## Online supplementary material

### Supplement A: Methods for computing the mRS of a virtual control arm

To compute the effectiveness of CTP based EVT patient selection a control arm that did not receive EVT is required (noEVT). Since we did not use randomized data, we computed the probability of specific mRS scores of a virtual control arm based on available treatment effect and treatment effect modification odds ratios on an ordinal scale. Sensitivity analyses were performed for varying values of these odds ratios. For the control arm mRS simulation we need to have the mRS and baseline characteristics an EVT treated patient, a distribution of a population treated with EVT and a control arm (we used the MR CLEAN trial data), and the OR for treatment effect ( $\hat{\omega}(mRS|EVT) = \hat{\omega}$  1.67) and treatment effect modification ( $\hat{\omega}(mRS|EVT * ICV) = \hat{\omega} 0.98$  per 10 mL) related to mRS. We assume in the example below a patient with mRS 2 after EVT with a core volume at baseline of 60 mL. The following steps were taken:

Based on the ORs we can compute the combined OR for a specific patient that received EVT as if she did not receive EVT (inverse of the OR: formula 1 and 2). Taking the natural log of an OR gives us the absolute mRS shift (formula 3). We can use this absolute shift to compute the effect on outcome of ICV ( $ICV(10\text{ mL}) \hat{\omega}$ ) and add this with the effect of noEVT to compute the combined OR (formula 4).

$$\hat{\omega}(mRS|noEVT) = \frac{1}{\hat{\omega}(mRS|EVT)}$$

Formula 1

$$\hat{\omega}(mRS|noEVT * ICV) = \frac{1}{\hat{\omega}(mRS|EVT * ICV)}$$

Formula 2

$$absolute\ mRS\ shift = \ln(\hat{\omega})$$

Formula 3

$$\hat{\omega}(mRS|noEVT \wedge ICV) = e^{\ln(\hat{\omega}(mRS|noEVT)) * 1 + \ln(\hat{\omega})}$$

Formula 4

For the next steps we use the  $\hat{\omega}(mRS|EVT)$  (=1.67), the total number of patients with EVT in the literature source for treatment effect (MR CLEAN trial  $n(EVT)=233$ ), the number of patient with EVT achieving  $mRS \leq 2$   $n(mRS \leq 2 \wedge EVT)$  (=77), the probability of the patients' mRS given EVT  $p(mRS \leq 2 | EVT)$  (=0.33), the total number of patients in the control arm  $n(noEVT)$  (=267), the number of patients in the control arm achieving  $mRS \leq 2$   $n(mRS \leq 2 \wedge noEVT)$  (=77), and the probability  $mRS \leq 2$  in the control arm  $p(mRS \leq 2 | noEVT)$  (=0.195). We use the probability and OR for  $mRS \leq 2$  to get stable estimates irrespective of the simulated patients' mRS; low sample sizes for mRS 0 and unreasonably large for mRS 6 resulting in inaccurate outcome simulations.

Based on the standard formulas to compute the OR (formulas 5-7) and the new computed combined OR based on literature OR and patient observations from formula 4, it is possible to derive formula 8 for computing  $Odds(mRS \leq 2 | noEVT)$ .

$$p(mRS \leq 2 | EVT) = \frac{n(mRS \leq 2 \wedge EVT)}{n_{total\ EVT}}$$

Formula 5

$$Odds(mRS \leq 2 | EVT) = \frac{p(mRS \leq 2 | EVT)}{1 - p(mRS \leq 2 | EVT)}$$

Formula 6

$$\zeta(mRS \leq 2 | EVT) = \frac{Odds(mRS \leq 2 | EVT)}{Odds(mRS \leq 2 | noEVT)}$$

Formula 7

$$Odds(mRS \leq 2 | noEVT) = Odds(mRS \leq 2 | EVT) * \zeta(mRS \leq 2 | EVT)$$

Formula 8

Finally, after combining formulas 5-8 using a patient specific OR from formula 4 you can compute the virtual probability of mRS shift in the control arm (formula 9 using formulas 5-8). The results per formula for our example are described in the section below formula 9. After solving formula 9, the value of  $p(mRS \leq 2 | noEVT)$  is used to compute a 1 point shift. In the example below, if a patient has an mRS of 3 with EVT, if no EVT was given she has a probability of 0.25 for an mRS of 3 and 0.75 for an mRS of 4.

$$p(mRS \leq 2 | noEVT) = (1 - p(mRS \leq 2 | noEVT)) * Odds(mRS \leq 2 | noEVT)$$

Formula 9

#### Example results:

$$\zeta(mRS | noEVT) = \frac{1}{1.67} = 0.60$$

Formula 1

$$\zeta(mRS | noEVT * ICV) = \frac{1}{0.98} = 1.02$$

Formula 2

$$\zeta(mRS | noEVT \wedge ICV) = e^{n(0.60) * 1 + \ln(1.02) * 6} = 0.67$$

Formula 4

$$p(mRS \leq 2 | EVT) = \frac{77}{233} = 0.33$$

Formula 5

$$Odds(mRS \leq 2 | EVT) = \frac{0.33}{1 - 0.33} = 0.49$$

Formula 6



$$\text{Odds}(mRS \leq 2 | \text{noEVT}) = 0.49 * 0.60 = 0.33$$

Formula 8

$$p(mRS \leq 2 | \text{noEVT}) = (1 - p(mRS \leq 2 | \text{noEVT})) * 0.33$$

Formula 9

$$1.33 * p(mRS \leq 2 | \text{noEVT}) = 0.33$$

$$p(mRS \leq 2 | \text{noEVT}) = \frac{0.33}{1.33} = 0.25$$

Solving formula 9

The probability of mRS scores for the no EVT arm could deviate from observed values in the MR CLEAN trial. This could be due to inaccuracies in the proportional odds assumption or due to different patient characteristics in the EVT arm compared to the no EVT arm.

**Supplement B: Protocol deviations**

The presented work is based on a previously published protocol paper and the corresponding protocol online (trial registration number: NL7974; [trialssearch.who.int/Trial2.aspx?TrialID=NL7974](https://trialssearch.who.int/Trial2.aspx?TrialID=NL7974)). Below are the deviations to the protocol described with motivation.

**Default odds ratio EVT effect**

In the protocol, we mistakenly reported a default scenario OR of 1.86 (95%CI:1.34-2.59) for EVT effect. This should have been 1.67 (95%CI:1.21-2.3) as reported as adjusted common OR in the MR CLEAN trial. Since a lower EVT effect is beneficial for the use of CTP for EVT patient selection (and findings were negative regardless) we used the OR of 1.67. In additional sensitivity analyses (table 1), the value of 1.97 was also considered.

**Probabilistic simulations**

We reduced the number of resamples from 10,000 to 1,000 for computational purposes. As the proportion of patients excluded for EVT was relatively low due to the low occurrence of unfavorable perfusion profiles, we altered the sampled cohort size of our initial simulation to the original cohort size (n=703) instead of 100.

**Analyses**

We included analyses for the core-penumbra mismatch ratio up to present a more complete overview of potential CTP uses. Furthermore, we added a 10-year follow-up horizon and a most favorable CTP scenario considering elderly (aged $\geq$ 80 years) with a low EVT effect and high effect modification due to CTP parameters. We found that these analyses were of added value as they are sometimes considered and, even in the extreme cases, did not alter the conclusion.

**Primary outcome measure**

Excluding patients for EVT resulted at best in a cost savings for a limited loss of health in a small group of patients in the simulated cohorts. Therefore,  $\Delta$ QALYs per patient as average over the simulated cohorts was often zero or close to zero resulting in an ICER ( $\Delta$ Costs/  $\Delta$ QALYs) going to infinity or impossible values (it is impossible to divide by zero). Thus, we chose to use the NMB as primary outcome measure as this metric is insensitive to zero or close to zero values for  $\Delta$ QALYs. In appendix G, the ICER for all simulations is also reported together with the  $\Delta$ Costs and  $\Delta$ QALYs.

**Supplement C: CTP acquisition, post-processing, and quality assessment**

CTP scans were acquired according to local acquisition protocols, which differed per study site. CTP was collected from the same stroke centers for all sources in CLEOPATRA. Perfusion analysis was centrally performed by a trained observer using syngo.via CT Neuro Perfusion (version VB40, Siemens Healthcare, Forchheim, Germany). The ICV was estimated using a threshold CBV  $<1.2$  mL/100 mL and the critically hypoperfused tissue (including penumbra) was defined as CBF  $<27$  mL/100 mL/min. **These approaches were chosen based on previous research which has shown that these settings have the best agreement with RAPID software, which is a commonly used perfusion analysis software also used for the HERMES analysis on CTP perfusion.** A default smoothing filter was applied (smoothing strength 10 mm). Visual quality assessment of the CTP results was performed by two experienced neuroradiologists ( $>10$  and  $>15$  years of experience). In patients with an estimated CTP ischemic core volume  $\geq 70$  mL, craniocaudal cropping of the core segmentation was performed by an experienced reader to remove obvious artifacts at the level of the skull base. Quality of the CTP data (i.e. Z-axis coverage of the brain, adequate tube voltage, adequate contrast bolus injection) was comparable between all data sources in CLEOPATRA. The penumbra (or mismatch) volume was defined as critically hypoperfused volume minus ischemic core volume. The core-penumbra mismatch ratio was calculated as the critically hypoperfused volume divided by the ischemic core volume.

**Supplement D: Model input variables**

The table below describes all the input variables used for modelling purposes. This table contains alterations from our previous publication.

Variable	Value	Distribution	Data source
EVT effect (odds ratio)	1.67 (95%CI:1.21-2.3) (baseline) 1.97 (95%CI:1.51-2.6) (upper) 1.37 (95%CI:0.91-2.0) (lower) 1.17 (95%CI:0.71-1.8) (very low) 2.49 (95%CI:1.76-3.53) (HERMES)	Log-normal	Berkhemer et al. Goyal et al.
EVT effect modification of core volume (ICV*EVT odds ratio)	0.98 (95%CI:0.881-1.091) (baseline) 0.93 (95%CI:0.831-1.041) 0.88 (95%CI:0.781-0.991)	Log-normal	New analysis HERMES data, Table D.2
EVT effect modification of core-penumbra mismatch ratio (MMR*EVT odds ratio)	1.010 (95%CI:0.994;1.560) (baseline) 1.060 (95%CI:1.044;1.610) 1.110 (95%CI:1.094;1.660)	Log-normal	New analysis HERMES data, Table D.3
CTP ischemic core volume treatment decision threshold	Varying between 0-150 per 10 mL 70 mL at baseline	Fixed value	Deterministic
CTP core-penumbra mismatch ratio treatment decision threshold	Varying between 1.2-2.4 per 0.2 1.8 at baseline	Fixed value	Deterministic
Baseline probability of stroke recurrence	Dependent on years after index ischemic stroke	Fixed value	Pennlert et al.
HR recurrent stroke	age and mRS dependent	Log-normal	Pennlert et al.
Baseline probability of death	age, gender and year dependent	Fixed value	Dutch Royal Actuarial Society
HR mortality (by mRS: 01/2/3/4/5)	1.54/2.17/3.18/4.55/6.55	Log-normal	Hong et al.
Inflation rate in % per year	% per year Assumed for 2022: 9%	Fixed value	Central Bureau of Statistics
Costs EVT*	€9924.50	Fixed value	Van den Berg et al.
Costs IVT*	€950.82	Fixed value	Van den Berg et al.
Costs of CTP*	€251.40	Fixed value	Estimated in protocol
Costs year 1 (by 90 day mRS: 01/2/3/4/5/6)*	33,402(31,930)/52,804(23,571)/82,452(35,333)/	Gamma	Van Voorst et al.

mean(std)	112,414(35,786)/96,640(30,463)/21,112(17,350)		
Costs year 2 (by 18 month mRS: 01/2/3/4/5/6)* mean(std)	5,934(15,918)/8,543(14,844)/19,235(15,999)/43,193(45,640)/56,425(24,252)/423(3,196)	Gamma	Van Voorst et al. **
Costs year 2 onward (by 18 month mRS: 01/2/3/4/5/6)* mean(std)	3,633(9,087)/7,318(13,770)/16,276(11,753)/31,037(19,928)/54,997(24,874)/374(3,118)	Gamma	Van Voorst et al. **
QALY (by mRS: 01/2/3/4/5/6) mean(std)	0.94(0.09)/0.80(0.17)/0.68(0.24)/0.39(0.26)/0.24(0.25)/0(0.01)	Beta	Van Voorst et al. **

**Table D.1. Data sources for model input parameter estimation.** EVT: endovascular treatment; HR: hazard ratio; IVT: intravenous thrombolysis; mRS: modified Rankin Scale score; OR: odds ratio. Std: Standard deviation. \*Costs are depicted for the reference year 2015. \*\*: Information is provided in the supplementary material of this publication.

### Cost and QALY data specification

Data described below has previously been published.

*Costs per unit of care:* The Dutch costing manual for health care research, hospital registration systems, and data published by the institute of Medical Technological Assessment (iMTA, Rotterdam, the Netherlands) were used to extract costs per unit of care for the reference year 2015. The total costs of acute care and follow-up healthcare costs were computed based on unit of care volume estimates. All acute costs were inflated by 42% to account for overhead costs of the hospital (iMTA guideline).

#### *Acute care units of care:*

*Costs for CTP (€251.50)* were estimated in the protocol paper: 10% additional costs for acute care personnel (€94), €129 for the CTP acquisition, and €20 for the CTP software license costs per patient. The total was inflated by 42% to account for overhead costs.

*Costs for endovascular treatment (€9924.50):* Costs for 1 CTA and NCCT scan were added. Personal costs included 1 (neuro-) interventionist, 1 anesthesiologist, 2 radiology assistants, 2 anesthesia assistants during 1.5 hours of treatment delivery. We assumed that all procedures were conducted with general anesthesia as this added only marginal costs. Material during the endovascular procedure was assumed to consist of thrombectomy materials (guide wire, balloon, stent retriever or aspiration device), angiographic materials, vascular closure devices, and heparin.

*Costs for intravenous thrombolysis (€950.82)* were added if patients received it. The costs of thrombolysis delivery were extracted from Medicijnkosten.nl 2016.

#### *Long-term costs*

The following cost of care were considered: In-hospital care use, outpatient clinic visits, rehabilitation, formal home care, and long-term institutionalized care. The units of these long-term posts were estimated with patient questionnaires and report forms, medical records, and the hospital information systems. We computed the costs per mRS at 3 months for the first year and at 18 months for the second year. The long-term costs of the third year onward were assumed the same as the costs for the second year without rehabilitation costs as rehabilitation beyond this period is generally discontinued due to a lack in evidence showing a benefit of long-term rehabilitation.

#### *Quality-adjusted life years per mRS sub-score*

QALYs were computed per mRS sub-score per year based on 391 patients with 2-year follow-up collected in a previous study. EuroQol5D (EQ5D) questionnaires were used to estimate an utility score between 0 and 1 at 3, 6, 9, 12, 18, and 24 months after acute ischemic stroke. For each unique mRS sub-score per patient the average over the utility scores was used to construct a QALY per mRS sub-score. These QALY values per mRS sub-scores were used

to compute the point estimates (mean and standard deviation) and distributions (table D.1.) required to compute costs and QALYs from simulated longitudinal mRS sub-scores.

We assumed that in the long-run the differences in costs and QALYs due to brain and vascular damage would occur irrespective of EVT administration and mRS sub-scores of the simulated patients. Therefore, long-term effects of secondary diseases such as dementia related to brain and vascular damage were not included in this study.

Effect	OR	Lower bound 95% CI	Upper bound 95% CI	p-value
Age (per 5 yr)	0.834	0.786	0.885	<0.001
NIHSS (per 5 pts)	0.815	0.699	0.949	0.009
Onset to randomization (per 30 min)	0.950	0.901	1.002	0.059
ASPECTS	1.077	0.979	1.185	0.127
Female gender	0.812	0.600	1.098	0.175
tPA administered	0.923	1.508	0.565	0.748
ICA (vs M2)	0.468	0.226	0.969	0.041
M1 (vs M2)	0.709	0.364	1.379	0.310
EVT (vs best medical management)	2.520	1.483	4.283	0.001
Ischaemic core volume (per 10 ml)	0.862	0.795	0.935	<0.001
EVT * Ischaemic core volume (per 10 ml)	0.980	0.881	1.091	0.717

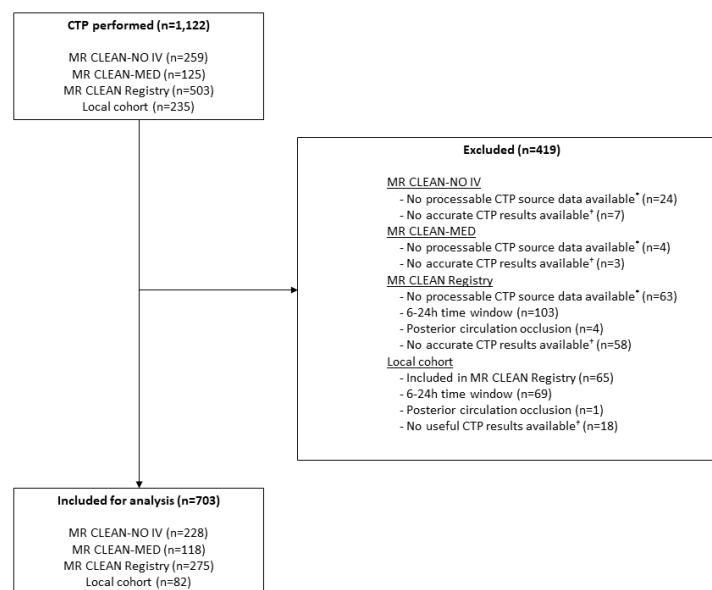
**Table D.2. Endovascular treatment effect modification for ordinal function outcome due to ischaemic core volume.** Presented results were extracted in a patient level analysis of the HERMES pooling. This analysis was similar to the one described by Campbell et al. . 95%CI: 95% confidence interval. ASPECTS: Alberta stroke program early CT score, NIHSS: National institute of health stroke. ICA: internal carotid artery. M1/M2: segments of middle cerebral artery. IVT: intravenous thrombolysis. EVT: endovascular treatment. MMR: core-penumbra mismatch ratio.

Effect	OR	Lower bound 95% CI	Upper bound 95% CI	p-value
Age (per 5 yr)	0.818	0.763	0.876	<0.0001
NIHSS (per 5 pts)	0.702	0.591	0.833	<0.0001
Onset to randomization (per 30 min)	0.959	0.905	1.017	0.164
ASPECTS	1.106	1.000	1.223	0.050
Female gender	0.967	0.695	1.346	0.844
IVT	0.994	0.584	1.693	0.983
ICA (vs M2)	0.385	0.172	0.861	0.020
M1 (vs M2)	0.553	0.264	1.159	0.116
EVT (vs best medical management)	1.984	1.055	3.730	0.033
MMR (per 1 point)	1.003	0.990	1.015	0.677
EVT * MMR (per 1 point)	1.010	0.994	1.026	0.228

**Table D.3. Endovascular treatment effect modification for ordinal function outcome due to mismatch ratio.**

Presented results were extracted in a patient level analysis of the HERMES pooling. This analysis was similar to the one described by Campbell et al. . Only patients with an ischaemic core volume > 0 were considered. 95%CI: 95% confidence interval. ASPECTS: Alberta stroke program early CT score, NIHSS: National institute of health stroke. ICA: internal carotid artery. M1/M2: segments of middle cerebral artery. IVT: intravenous thrombolysis. EVT: endovascular treatment. MMR: core-penumbra mismatch ratio.

## Supplement E: Inclusion and baseline characteristics



**Figure E1. Flowchart of patient selection.** CTP: CT perfusion. \*CTP source data without time information or CTP source data not available due to local storage in primary stroke centre. †Reasons for inaccurate CTP results include severe patient motion, severe curve truncation, no timely contrast arrival or incorrect timing CTP, or severe artefacts in CTP source data.



Variables	Values
Age median (IQR)	72 (62;81)
Male sex number (%)	391 (55.6%)
Baseline NIHSS median (IQR)	15 (9;19)
mRS before AIS number (%)	
0	404 (64.4%)
1	116 (18.5%)
2	63 (10.0%)
≥3	44 (7.0%)
Baseline ASPECTS median (IQR)	9 (8;10)
Baseline collateral score number (%)	
0	30 (4.8%)
1	191 (30.9%)
2	281 (45.4%)
3	117 (18.9%)
Occlusion location number (%)	
ICA	41 (5.8%)
ICA-T	127 (18.1%)
M1	367 (52.4%)
M2	166 (23.7%)
Ischaemic core volume in mL median (IQR)	13 (5;33)
Penumbra volume in mL Mean (SD)	113 (128)
Core-penumbra mismatch ratio median (IQR)	9 (4;19)
Onset-to-groin time in minutes median (IQR)	158 (115;230)
Duration of procedure in minutes median (IQR)	48 (31;71)
Received intravenous treatment with alteplase (0.9mg/kg) number (%)	382 (67.0%)
mRS 90-days after EVT number (%)	
0	47 (7.3%)
1	116 (17.9%)
2	154 (23.8%)
3	70 (10.8%)
4	76 (11.7%)

5	42 (6.5%)
6	142 (21.9%)

**Table E1: Baseline characteristics of the included cohort.** Abbreviations: IQR: interquartile range, SD: standard deviation, ASPECTS: Alberta stroke programme early CT score, NIHSS: National institute of health stroke, mRS: modified Rankin Scale, AIS: acute ischemic stroke, eTICI: extended Thrombolysis in Cerebral Ischemia.

Variable	Ischemic core volume (mL) subgroup									p-value
	≤10	10-20	20-30	30-40	40-50	50-70	70-90	90-110	≥110	
Number of patients	301	134	78	54	30	35	33	14	23	
Age (median - IQR)	71 (61;80)	73 (65;83)	69 (64;81)	68 (56;80)	72 (60;76)	74 (64;82)	65 (57;76)	66 (48;74)	73 (68;79)	0.13
Sex										<1e-5
Female	169 (56.5%)	59 (44.0%)	24 (31.2%)	14 (25.9%)	9 (30.0%)	13 (37.1%)	11 (33.3%)	5 (35.7%)	6 (26.1%)	
Male	130 (43.5%)	75 (56.0%)	53 (68.8%)	40 (74.1%)	21 (70.0%)	22 (62.9%)	22 (66.7%)	9 (64.3%)	17 (73.9%)	
Baseline NIHSS (median - IQR)	12 (7;17)	15 (10;19)	16 (11;19)	17 (13;20)	18 (14;22)	20 (16;22)	20 (17;23)	17 (16;21)	19 (17;23)	<1e-5
mRS prior to AIS										0.92
0	161 (60.8%)	81 (66.4%)	49 (73.1%)	29 (61.7%)	19 (65.5%)	19 (61.3%)	23 (74.2%)	8 (66.7%)	15 (68.2%)	
1	57 (21.5%)	22 (18.0%)	9 (13.4%)	8 (17.0%)	5 (17.2%)	5 (16.1%)	4 (12.9%)	2 (16.7%)	3 (13.6%)	
2	31 (11.7%)	9 (7.4%)	6 (9.0%)	7 (14.9%)	3 (10.3%)	4 (12.9%)	2 (6.5%)	0 (0.0%)	1 (4.5%)	
≥3	16 (6.0%)	10 (8.2%)	3 (4.5%)	3 (6.4%)	2 (6.9%)	3 (9.7%)	2 (6.5%)	2 (16.7%)	3 (13.6%)	
Baseline ASPECTS (median-IQR)	10 (9;10)	9 (8;10)	9 (7;10)	9 (7;10)	9 (8;9)	8 (6;10)	9 (7;10)	9 (7;9)	8 (5;10)	<1e-5
Baseline collateral score										<1e-5
0	1 (0.4%)	3 (2.5%)	4 (6.0%)	3 (6.5%)	0 (0.0%)	4 (12.9%)	4 (12.5%)	2 (15.4%)	9 (40.9%)	
1	47 (17.9%)	31 (26.1%)	23 (34.3%)	21 (45.7%)	14 (53.8%)	16 (51.6%)	21 (65.6%)	9 (69.2%)	9 (40.9%)	
2	145 (55.3%)	60 (50.4%)	30 (44.8%)	18 (39.1%)	8 (30.8%)	8 (25.8%)	7 (21.9%)	2 (15.4%)	2 (9.1%)	
3	69 (26.3%)	25 (21.0%)	10 (14.9%)	4 (8.7%)	4 (15.4%)	3 (9.7%)	0 (0.0%)	0 (0.0%)	2 (9.1%)	
Occlusion location										<0.001
ICA	19 (6.3%)	11 (8.2%)	4 (5.2%)	1 (1.9%)	2 (6.7%)	0 (0.0%)	1 (3.0%)	1 (7.1%)	2 (8.7%)	
ICA-T	41 (13.7%)	16 (11.9%)	17 (22.1%)	10 (18.5%)	4 (13.3%)	14 (40.0%)	10 (30.3%)	6 (42.9%)	9 (39.1%)	
M1	169 (56.3%)	73 (54.5%)	31 (40.3%)	32 (59.3%)	13 (43.3%)	16 (45.7%)	20 (60.6%)	4 (28.6%)	9 (39.1%)	
M2	71 (23.7%)	34 (25.4%)	25 (32.5%)	11 (20.4%)	11 (36.7%)	5 (14.3%)	2 (6.1%)	3 (21.4%)	3 (13.0%)	
Ischemic core volume in mL (median - IQR)	4 (2;7)	14 (12;17)	24 (22;27)	35 (33;38)	45 (43;48)	61 (57;66)	77 (72;82)	94 (92;100)	154 (123;196)	<1e-5
Penumbra volume in mL (mean - SD)	107 (188)	110 (51)	119 (48)	116 (45)	132 (45)	124 (55)	126 (43)	131 (44)	108 (53)	0.95
Core-penumbra mismatch ratio (median - IQR)	19 (13;36)	9 (6;12)	6 (5;8)	4 (3;5)	4 (3;5)	3 (2;4)	3 (2;4)	2 (2;2)	2 (2;2)	<0.001
Onset to groin time in minutes	155 (115;225)	162 (122;254)	145 (115;209)	158 (111;212)	158 (117;226)	165 (110;194)	192 (125;307)	163 (120;195)	166 (118;212)	0.83

(median - IQR)										
<b>Duration of procedure in minutes (median - IQR)</b>	49 (31;75)	40 (30;66)	42 (29;62)	56 (28;83)	47 (32;61)	55 (39;80)	50 (35;64)	55 (40;85)	56 (40;66)	0.60
<b>Intravenous thrombolysis administration</b>										0.44
<b>No</b>	69 (28.5%)	40 (36.7%)	22 (33.8%)	12 (27.3%)	11 (42.3%)	13 (48.1%)	11 (39.3%)	4 (36.4%)	6 (33.3%)	
<b>Yes</b>	173 (71.5%)	69 (63.3%)	43 (66.2%)	32 (72.7%)	15 (57.7%)	14 (51.9%)	17 (60.7%)	7 (63.6%)	12 (66.7%)	
<b>mRS 90-days after EVT</b>										<0.001
<b>0</b>	30 (10.7%)	9 (7.3%)	2 (2.9%)	3 (6.4%)	1 (3.8%)	0 (0.0%)	2 (6.1%)	0 (0.0%)	0 (0.0%)	
<b>1</b>	58 (20.7%)	26 (21.1%)	16 (23.2%)	8 (17.0%)	3 (11.5%)	1 (3.1%)	4 (12.1%)	0 (0.0%)	0 (0.0%)	
<b>2</b>	78 (27.9%)	30 (24.4%)	16 (23.2%)	11 (23.4%)	4 (15.4%)	4 (12.5%)	8 (24.2%)	1 (7.1%)	2 (9.1%)	
<b>3</b>	26 (9.3%)	14 (11.4%)	9 (13.0%)	4 (8.5%)	5 (19.2%)	3 (9.4%)	5 (15.2%)	3 (21.4%)	1 (4.5%)	
<b>4</b>	23 (8.2%)	19 (15.4%)	7 (10.1%)	8 (17.0%)	4 (15.4%)	4 (12.5%)	7 (21.2%)	3 (21.4%)	1 (4.5%)	
<b>5</b>	21 (7.5%)	4 (3.3%)	3 (4.3%)	2 (4.3%)	2 (7.7%)	3 (9.4%)	3 (9.1%)	1 (7.1%)	3 (13.6%)	
<b>6</b>	44 (15.7%)	21 (17.1%)	16 (23.2%)	11 (23.4%)	7 (26.9%)	17 (53.1%)	4 (12.1%)	6 (42.9%)	15 (68.2%)	

**Table E2: Baseline characteristics of the CLEOPATRA population per 10 mL ischemic core volume.**

Abbreviations: IQR: interquartile range, SD: standard deviation, ASPECTS: Alberta stroke programme early CT score, NIHSS: National institute of health stroke, mRS: modified Rankin Scale, AIS: acute ischemic stroke, eTICI: extended Thrombolysis in Cerebral Ischemia.

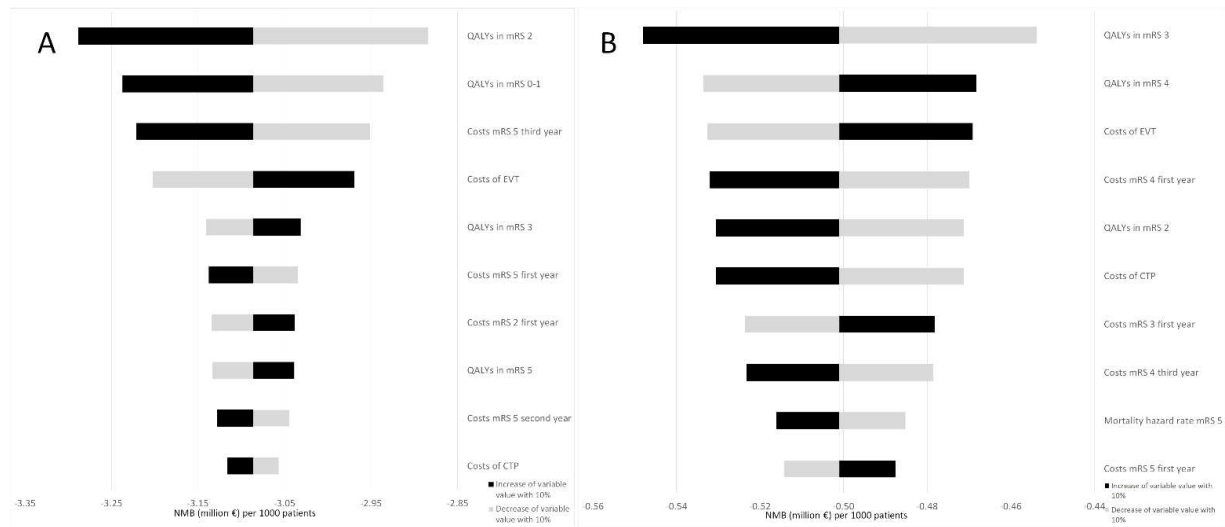
Variable	Core-penumbra mismatch ratio (penumbra volume/core volume)							p-value
	<=1.4	1.4-1.6	1.6-1.8	1.8-2.0	2.0-2.2	2.2-2.4	>=2.4	
Number of patients	5	6	8	11	15	19	635	
Age (median - IQR)	80 (71;81)	72 (69;75)	69 (50;79)	73 (58;78)	64 (63;82)	68 (58;73)	72 (62;81)	0.66
Sex								0.32
Female	3 (60.0%)	1 (16.7%)	3 (37.5%)	2 (18.2%)	7 (46.7%)	6 (31.6%)	287 (45.2%)	
Male	2 (40.0%)	5 (83.3%)	5 (62.5%)	9 (81.8%)	8 (53.3%)	13 (68.4%)	348 (54.8%)	
Baseline NIHSS (median - IQR)	18 (15;25)	18 (18;22)	20 (16;23)	18 (16;20)	17 (16;20)	18 (13;20)	15 (9;19)	<0.01
mRS prior to AIS								0.85
0	2 (50.0%)	4 (66.7%)	6 (75.0%)	8 (80.0%)	7 (58.3%)	11 (64.7%)	364 (64.3%)	
1	1 (25.0%)	1 (16.7%)	1 (12.5%)	1 (10.0%)	1 (8.3%)	2 (11.8%)	107 (18.9%)	
2	1 (25.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	2 (16.7%)	1 (5.9%)	58 (10.2%)	
≥3	0 (0.0%)	0 (0.0%)	1 (12.5%)	1 (10.0%)	2 (16.7%)	3 (17.6%)	37 (6.5%)	
Baseline ASPECTS (median-IQR)	8 (5;8)	10 (7;10)	8 (8;9)	10 (7;10)	10 (8;10)	8 (7;10)	9 (8;10)	0.07
Baseline collateral score								<1e-5
0	4 (80.0%)	3 (60.0%)	2 (25.0%)	1 (12.5%)	0 (0.0%)	1 (5.3%)	19 (3.4%)	
1	1 (20.0%)	2 (40.0%)	3 (37.5%)	5 (62.5%)	6 (42.9%)	12 (63.2%)	161 (29.0%)	
2	0 (0.0%)	0 (0.0%)	2 (25.0%)	2 (25.0%)	6 (42.9%)	5 (26.3%)	265 (47.7%)	
3	0 (0.0%)	0 (0.0%)	1 (12.5%)	0 (0.0%)	2 (14.3%)	1 (5.3%)	111 (20.0%)	
Occlusion location								0.12
ICA	0 (0.0%)	1 (16.7%)	0 (0.0%)	1 (9.1%)	2 (13.3%)	0 (0.0%)	37 (5.8%)	
ICA-T	4 (80.0%)	1 (16.7%)	2 (25.0%)	3 (27.3%)	4 (26.7%)	6 (31.6%)	107 (16.9%)	
M1	1 (20.0%)	3 (50.0%)	4 (50.0%)	3 (27.3%)	5 (33.3%)	8 (42.1%)	342 (54.0%)	
M2	0 (0.0%)	1 (16.7%)	2 (25.0%)	4 (36.4%)	4 (26.7%)	5 (26.3%)	147 (23.2%)	
Ischemic core volume in mL (median - IQR)	208 (184;246)	157 (132;200)	109 (94;121)	43 (18;70)	64 (45;88)	70 (39;87)	12 (5;26)	<1e-5
Penumbra volume in mL (mean - SD)	78 (25)	89 (33)	76 (23)	71 (44)	86 (31)	82 (35)	116 (134)	0.60
Onset to groin time in minutes (median - IQR)	225 (145;268)	166 (116;197)	158 (118;194)	135 (120;172)	182 (146;239)	177 (145;272)	155 (115;230)	0.72
Duration of procedure in minutes (median - IQR)	60 (30;66)	52 (40;60)	55 (43;89)	56 (42;72)	54 (30;62)	62 (38;90)	47 (30;71)	0.57
Intravenous thrombolysis administration								0.12
No	3 (75.0%)	0 (0.0%)	1 (14.3%)	1 (14.3%)	5 (35.7%)	9 (52.9%)	168 (32.6%)	

Yes	1 (25.0%)	3 (100.0%)	6 (85.7%)	6 (85.7%)	9 (64.3%)	8 (47.1%)	347 (67.4%)	
<b>mRS 90-days after EVT</b>								<0.0001
<b>0</b>	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	46 (7.9%)	
<b>1</b>	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (27.3%)	0 (0.0%)	1 (5.9%)	112 (19.2%)	
<b>2</b>	0 (0.0%)	1 (16.7%)	0 (0.0%)	1 (9.1%)	2 (14.3%)	2 (11.8%)	146 (25.1%)	
<b>3</b>	1 (20.0%)	0 (0.0%)	2 (25.0%)	0 (0.0%)	1 (7.1%)	2 (11.8%)	64 (11.0%)	
<b>4</b>	0 (0.0%)	0 (0.0%)	1 (12.5%)	0 (0.0%)	4 (28.6%)	4 (23.5%)	67 (11.5%)	
<b>5</b>	0 (0.0%)	0 (0.0%)	2 (25.0%)	1 (9.1%)	0 (0.0%)	3 (17.6%)	36 (6.2%)	
<b>6</b>	4 (80.0%)	5 (83.3%)	3 (37.5%)	5 (45.5%)	7 (50.0%)	5 (29.4%)	111 (19.1%)	

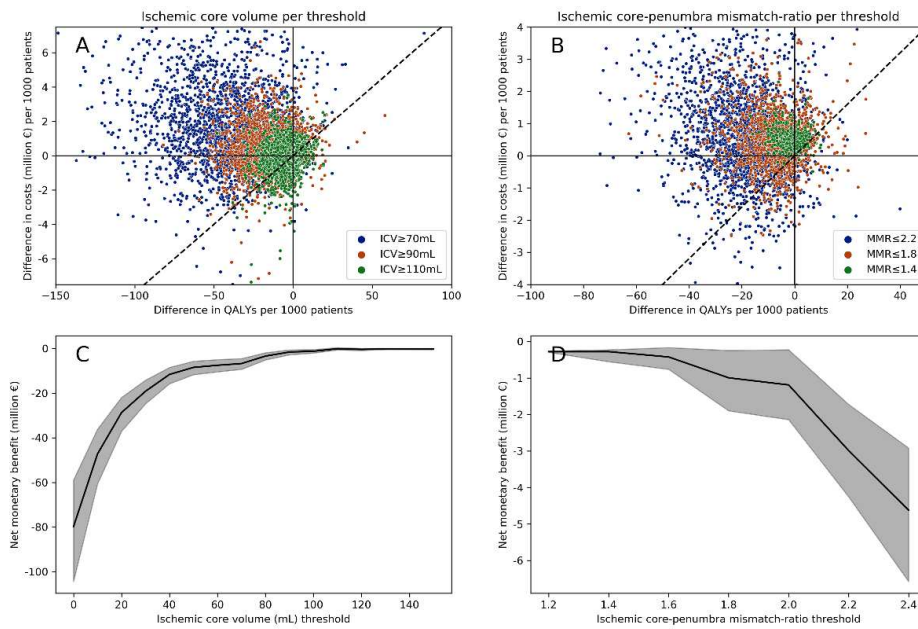
**Table E3: Baseline characteristics of the CLEOPATRA population by core-penumbra mismatch ratio.** For 4 patients to mismatch ratio values were available. Abbreviations: IQR: interquartile range, SD: standard deviation, ASPECTS: Alberta stroke program early CT score, NIHSS: National institute of health stroke, mRS: modified Rankin Scale, AIS: acute ischemic stroke, eTICI: extended Thrombolysis in Cerebral Ischemia.

### Supplement F: Extended result figures for CTP based EVT selection

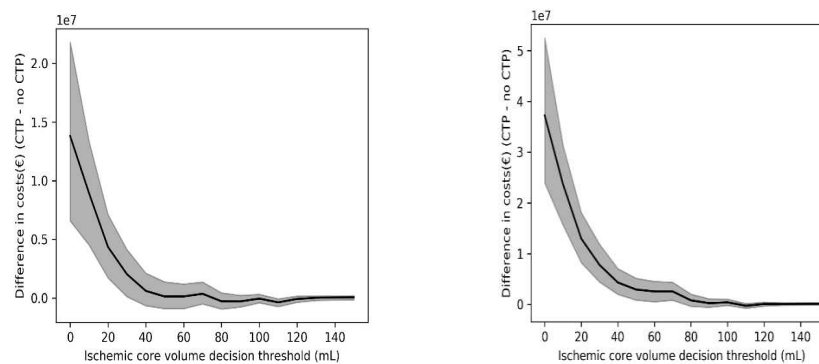
Extended sensitivity analyses considering extended horizon simulations (10 year), per decision threshold the outcome measures, extended measures for the per OR increase or decrease of EVT effect and ICV or MMR based effect modification.



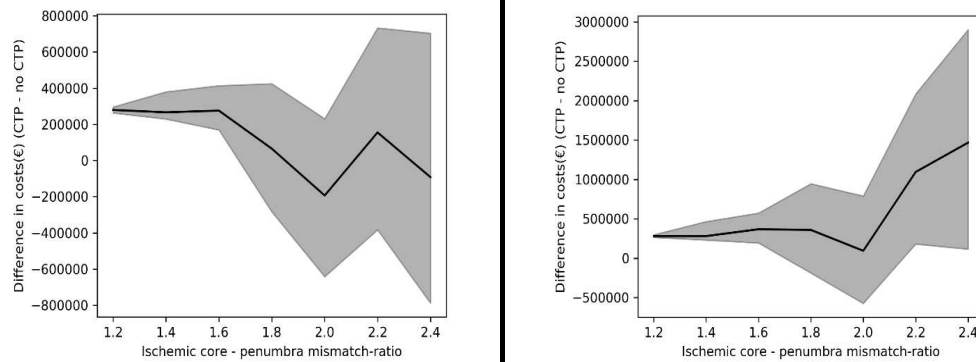
**Figure F.1: Tornado diagram of the one-way sensitivity analyses.** Changes in NMB due to a 10% increase (black) and decrease (gray) relative to the baseline simulation for the 10 most influential model input variables. The input ORs for EVT effect, ICV-, and MMR-based EVT effect modification were not considered in the one-way sensitivity analyses. A 5-year horizon was used. 3A: One-way sensitivity analysis using a baseline ICV threshold of  $\geq 70$  mL to exclude patients for EVT. 3B: One-way sensitivity analysis using a baseline MMR threshold of  $\leq 1.8$  to exclude patients for EVT. NMB: net monetary benefit at a willingness to pay of €80,000 per QALY. ICV: ischemic core volume. EVT: endovascular treatment. QALY: quality-adjusted life-years. mRS: modified Rankin Scale. CTP: CT perfusion. EVT: endovascular treatment.



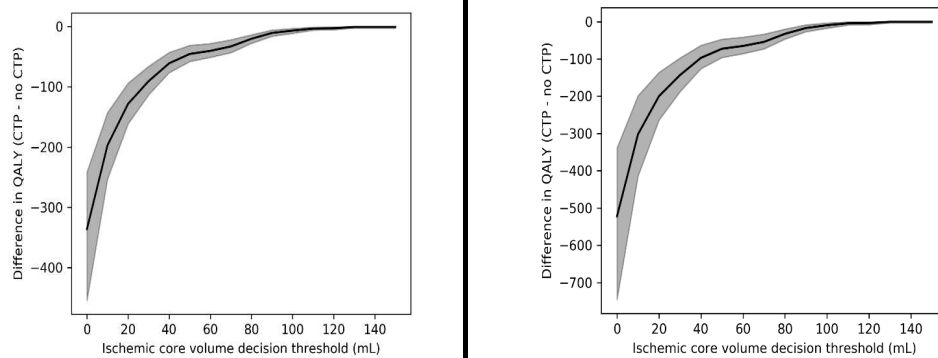
**Figure F.2: 10-year follow-up horizon baseline PSA results per 1000 patients.** This figure is similar to figure 2 in the main article but with 10-year follow-up.



**Figure F.3: ΔCosts per ischemic core volume threshold per 1000 patients.** Values are presented as median with IQR for the baseline PSA in €10,000,000 per 1000 patients. Left: 5-year follow-up. Right: 10 year follow-up.

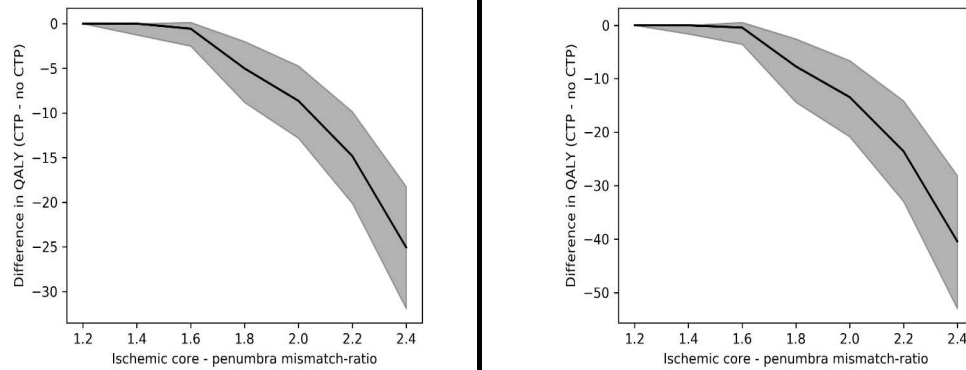


**Figure F.4:**  $\Delta$ Costs per core-penumbra mismatch ratio threshold per 1000 patients. Values are presented as median with IQR for the baseline PSA. Left: 5-year follow-up. Right: 10 year follow-up.

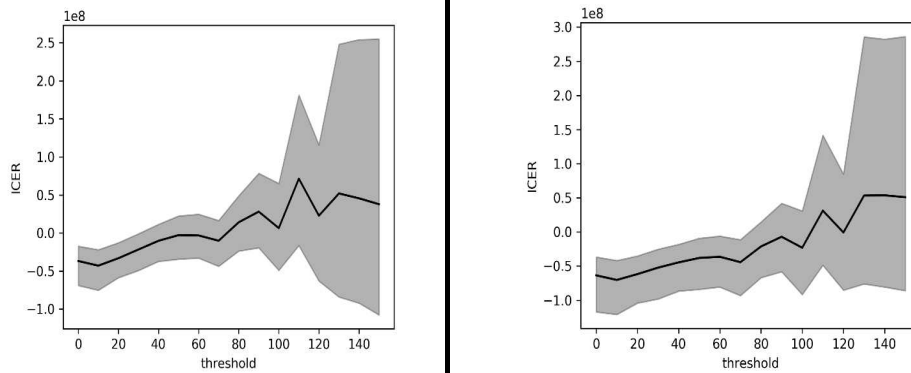


**Figure F.5:**  $\Delta$ QALYs per ischemic core volume decision threshold per 1000 patients. Values are presented as median with IQR for the baseline PSA. Left: 5-year follow-up. Right: 10 year follow-up.

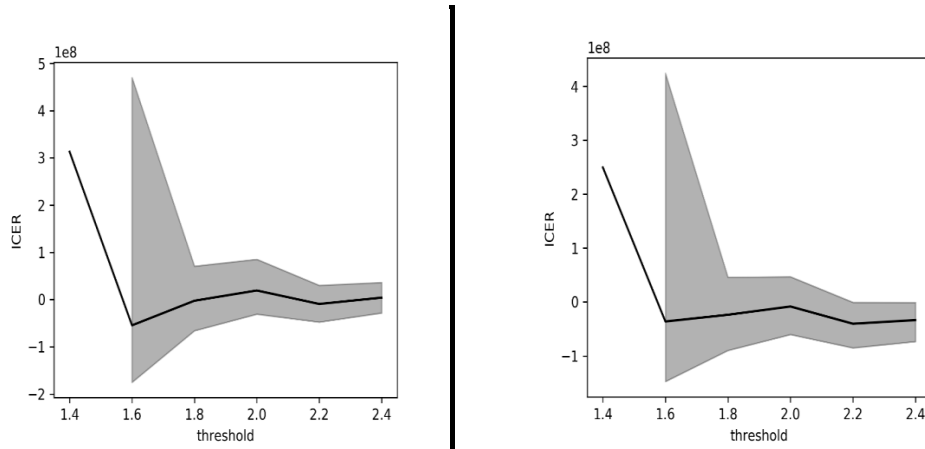




**Figure F.6:  $\Delta$ QALYs per core-penumbra mismatch ratio threshold per 1000 patients.** Values are presented as median with IQR for the baseline PSA. Left: 5-year follow-up. Right: 10-year follow-up.



**Figure F.7: ICER per ischemic core volume threshold per 1000 patients.** Values are presented as median with IQR for the baseline PSA **in 100,000,000** per 1000 patients. Left: 5-year follow-up. Right: 10-year follow-up.



**Figure F.8: ICER per core-penumbra mismatch ratio threshold per 1000 patients.** Values are presented as median with IQR for the baseline PSA. Left: 5-year follow-up. Right: 10-year follow-up.

**Supplement G: Extended results table**

CTP measure	Years of follow-up	OREVT effect (change relative to 1.67[95% CI : 1.21-2.3])	OR effect modification (change relative to baseline)*	ICER Median (IQR)	NMB (€) Median (IQR)	ΔQALYs Median (IQR)	ΔCosts (€) Median (IQR)
	5	-0.5	-0.1	57035 (-81387;213725)	44361 (-84207;180651)	-0.576 (-1.709;0.026)	-98566 (-244442;14011)
	5	-0.5	-0.05	54204 (-52029;194974)	52532 (-158294;247178)	-1.324 (-3.112;-0.124)	-150364 (-394145;15489)
	5	-0.5	0	63571 (-27445;182863)	75260 (-256606;356220)	-2.55 (-4.962;-0.677)	-262666 (-589364;-24891)
	5	-0.4	-0.1	56112 (-80919;202785)	43761 (-91557;186341)	-0.634 (-1.82;0.01)	-103520 (-257824;14687)
	5	-0.4	-0.05	56048 (-47465;191643)	55220 (-167300;258060)	-1.454 (-3.342;-0.17)	-162788 (-413780;14303)
	5	-0.4	0	67394 (-22823;181803)	84206 (-267820;369916)	-2.748 (-5.202;-0.77)	-282565 (-621968;-31396)
	5	-0.3	-0.1	56115 (-79143;200186)	45137 (-97373;189920)	-0.697 (-1.918;-0.0)	-108139 (-272493;15091)
	5	-0.3	-0.05	56816 (-45700;187411)	58740 (-171751;270871)	-1.584 (-3.53;-0.199)	-172610 (-434498;12927)
	5	-0.3	0	68218 (-19427;182480)	92540 (-274492;387168)	-2.878 (-5.369;-0.866)	-300255 (-646764;-37602)
	5	-0.2	-0.1	56679 (-75842;199414)	47333 (-103038;198221)	-0.77 (-2.025;-0.001)	-113113 (-283348;14654)
	5	-0.2	-0.05	58023 (-42033;194116)	61656 (-175985;281418)	-1.702 (-3.679;-0.254)	-182325 (-454905;6496)
	5	-0.2	0	69736 (-17511;185504)	97328 (-279658;406186)	-3.019 (-5.561;-0.943)	-317090 (-671630;-42393)
	5	-0.1	-0.1	56879 (-72084;201236)	50367 (-108819;203738)	-0.829 (-2.136;-0.009)	-117656 (-297047;15480)
	5	-0.1	-0.05	61153 (-40076;198122)	66147 (-177890;288937)	-1.787 (-3.829;-0.287)	-190396 (-472011;148)
	5	-0.1	0	70378 (-16496;182958)	100154 (-282228;416840)	-3.151 (-5.749;-0.998)	-333259 (-693926;-46221)
	5	0	-0.1	55947 (-71851;202198)	52380 (-117014;211993)	-0.894 (-2.251;-0.023)	<b>-123386 (-309257;13828)</b>
	5	0	-0.05	63146 (-36895;198058)	71360 (-189586;298635)	-1.867 (-3.982;-0.332)	-200018 (-490399;-1770)
	5	0	0	71346 (-16517;181241)	102227 (-282942;431923)	-3.27 (-5.874;-1.052)	<b>-348966 (-712406;-51158)</b>
	5	0.1	-0.1	56200 (-69553;200735)	54241 (-124656;220749)	-0.961 (-2.349;-0.033)	-128429 (-320794;15006)
	5	0.1	-0.05	65735 (-34476;195958)	75914 (-193954;308028)	-1.959 (-4.127;-0.371)	-215795 (-506732;-4882)
	5	0.1	0	73472 (-12106;182197)	105745 (-283315;447098)	-3.38 (-6.055;-1.102)	-366110 (-725442;-54417)
	5	0.2	-0.1	57846 (-67800;200167)	55301 (-128324;225883)	-1.022 (-2.449;-0.043)	-134942 (-331458;14009)
	5	0.2	-0.05	67269 (-31691;194190)	77932 (-195506;318772)	-2.055 (-4.28;-0.404)	-226367 (-520125;-7100)
	5	0.2	0	74175 (-10997;181061)	107731 (-281118;460564)	-3.502 (-6.225;-1.146)	-378798 (-740749;-58667)
	5	0.3	-0.1	57417 (-66942;196961)	57805 (-131228;233197)	-1.085 (-2.556;-0.05)	-139714 (-344263;14650)
	5	0.3	-0.05	65110 (-31006;189307)	81540 (-202099;334318)	-2.154 (-4.414;-0.454)	-232732 (-535444;-8026)
	5	0.3	0	75009 (-10030;180919)	115014 (-282947;472304)	-3.624 (-6.366;-1.188)	-393648 (-754846;-64458)
	5	0.82	-0.1	58939 (-57998;197632)	69596 (-146628;265746)	-1.354 (-3.068;-0.099)	-158741 (-397187;9673)
	5	0.82	-0.05	72948 (-19370;189290)	95139 (-235410;378627)	-2.588 (-5.031;-0.654)	-284265 (-621398;-23967)
ICV≥110mL	5	0.82	0	79288 (-3228;187236)	126436 (-294179;516591)	-4.0 (-6.968;-1.43)	-436485 (-823877;-86247)

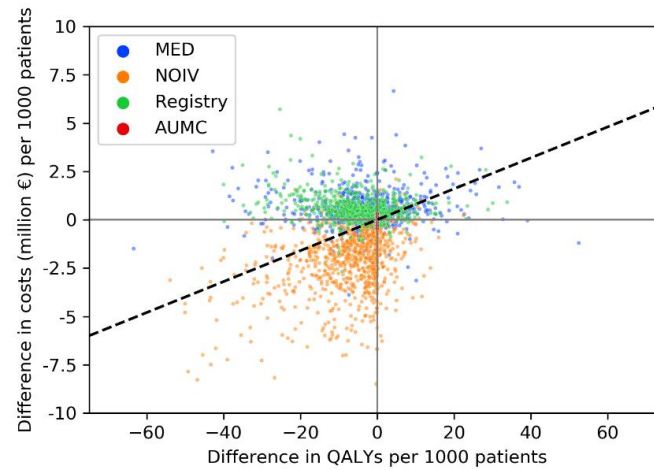
	10	-0.5	-0.1	13924 (-107627;147588)	-24078 (-262408;153870)	-0.174 (-1.797;1.033)	8203 (-149320;225180)
	10	-0.5	-0.05	15434 (-95929;151501)	-82733 (-430820;215513)	-0.994 (-3.999;0.927)	-14184 (-291235;270693)
	10	-0.5	0	22562 (-68585;136198)	-119896 (-587168;333612)	-2.981 (-7.277;-0.044)	-145266 (-568643;244701)
	10	-0.4	-0.1	14070 (-110030;145371)	-30516 (-281916;157278)	-0.225 (-1.947;1.015)	8908 (-156743;226729)
	10	-0.4	-0.05	14205 (-97628;144677)	-85256 (-447245;233845)	-1.133 (-4.292;0.867)	-24232 (-316069;269778)
	10	-0.4	0	23605 (-66187;137205)	-119281 (-603941;345315)	-3.309 (-7.651;-0.159)	-167871 (-589762;239434)
	10	-0.3	-0.1	15407 (-107006;150976)	-38411 (-295091;163770)	-0.278 (-2.135;1.022)	8637 (-166152;237296)
	10	-0.3	-0.05	16365 (-91996;145559)	-89848 (-460125;247493)	-1.297 (-4.514;0.728)	-36184 (-338417;262836)
	10	-0.3	0	25893 (-60577;139203)	-112504 (-620679;366957)	-3.537 (-7.982;-0.262)	-186259 (-618667;225119)
	10	-0.2	-0.1	17228 (-106133;153708)	-42180 (-307595;172895)	-0.331 (-2.308;1.035)	4985 (-174070;240083)
	10	-0.2	-0.05	15346 (-92066;137154)	-95364 (-476997;258349)	-1.465 (-4.817;0.664)	-43509 (-360974;259447)
	10	-0.2	0	27653 (-55784;139526)	-112212 (-626647;382943)	-3.811 (-8.364;-0.363)	-209420 (-653387;214308)
	10	-0.1	-0.1	15957 (-107522;149440)	-44065 (-317094;179724)	-0.422 (-2.488;1.012)	2557 (-189977;245799)
	10	-0.1	-0.05	18261 (-90217;139386)	-95683 (-492351;262064)	-1.633 (-4.989;0.618)	-60346 (-382490;258983)
	10	-0.1	0	29231 (-53582;138694)	-104584 (-638723;405304)	-4.097 (-8.698;-0.535)	-228620 (-690705;204550)
	10	0	-0.1	16219 (-102805;158664)	-47193 (-327253;184168)	-0.499 (-2.652;1.017)	-3120 (-203254;249522)
	10	0	-0.05	18948 (-88290;138981)	-95305 (-508231;268169)	-1.773 (-5.295;0.527)	-68605 (-407677;258424)
	10	0	0	31244 (-48780;141749)	-97781 (-644889;420136)	-4.346 (-9.065;-0.651)	-246679 (-733714;191840)
	10	0.1	-0.1	17184 (-99660;163819)	-51098 (-344249;189337)	-0.583 (-2.793;1.008)	-5263 (-215647;247064)
	10	0.1	-0.05	19639 (-82503;140040)	-96881 (-507471;275083)	-2.018 (-5.559;0.386)	-81194 (-436340;259133)
	10	0.1	0	32885 (-47053;141486)	-101056 (-650787;437771)	-4.57 (-9.35;-0.772)	-269124 (-774042;181113)
	10	0.2	-0.1	16340 (-103000;159953)	-54225 (-357808;198961)	-0.659 (-2.958;0.995)	-8581 (-234230;252198)
	10	0.2	-0.05	21703 (-81096;141291)	-98816 (-513571;288845)	-2.183 (-5.814;0.318)	-93835 (-453393;252877)
	10	0.2	0	34370 (-44782;141426)	-105302 (-654179;447107)	-4.801 (-9.596;-0.88)	-280358 (-806374;169203)
	10	0.3	-0.1	16328 (-101862;158015)	-56497 (-369169;205562)	-0.737 (-3.073;0.98)	-10532 (-253472;253672)
	10	0.3	-0.05	23106 (-76081;144383)	-94125 (-521341;297295)	-2.323 (-6.048;0.222)	-103309 (-475934;249412)
	10	0.3	0	35650 (-44191;141302)	-103484 (-659676;460891)	-5.018 (-9.771;-0.999)	-295151 (-832410;151728)
	10	0.82	-0.1	15440 (-103939;153179)	-69079 (-415466;234382)	-1.061 (-3.901;0.865)	-32815 (-315893;259125)
	10	0.82	-0.05	25928 (-65763;137779)	-96801 (-565620;347538)	-3.099 (-7.207;-0.016)	-160655 (-571570;220386)
	10	0.82	0	39788 (-38956;141756)	-74712 (-685404;519196)	-5.824 (-10.778;-1.566)	-373317 (-951864;101952)
MMR≤1.4	5	-0.5	0	380124 (-151368;-2147483648)	-263889 (-433414;-222141)	0.0 (-0.976;0.0)	272937 (229403;377940)
	5	-0.5	0.05	380566 (-151071;-2147483648)	-264070 (-433655;-222185)	0.0 (-0.98;0.0)	272851 (229403;377990)
	5	-0.5	0.1	380991 (-)	-264073 (-)	0.0 (-)	272766

			150789;- 2147483648)	433887;-222227)	0.984;0.0)	(229403;378038)
5	-0.4	0	361345 (- 149258;- 2147483648)	-264242 (- 438308;-223070)	0.0 (- 1.053;0.0)	271425 (229403;379180)
5	-0.4	0.05	361774 (- 149006;- 2147483648)	-264427 (- 438604;-223111)	0.0 (- 1.056;0.0)	271334 (229403;379217)
5	-0.4	0.1	362187 (- 148728;- 2147483648)	-264604 (- 438887;-223151)	0.0 (- 1.058;0.0)	271247 (229403;379252)
5	-0.3	0	349751 (- 145069;- 2147483648)	-267393 (- 443666;-225803)	0.0 (- 1.092;0.0)	269980 (229403;379943)
5	-0.3	0.05	350047 (- 144842;- 2147483648)	-267548 (- 444090;-225943)	0.0 (- 1.094;0.0)	269887 (229403;379994)
5	-0.3	0.1	350331 (- 144625;- 2147483648)	-267696 (- 444428;-226076)	0.0 (- 1.096;0.0)	269798 (229403;380042)
5	-0.2	0	330581 (- 143474;- 2147483648)	-270117 (- 449671;-225297)	0.0 (- 1.152;0.0)	268606 (229403;380813)
5	-0.2	0.05	330819 (- 143169;- 2147483648)	-270291 (- 449886;-225155)	0.0 (- 1.156;0.0)	268513 (229403;380856)
5	-0.2	0.1	331047 (- 142878;- 2147483648)	-270600 (- 450092;-225020)	0.0 (-1.16;0.0)	268423 (229403;380881)
5	-0.1	0	311909 (- 143710;- 2147483648)	-276027 (- 453103;-227992)	0.0 (- 1.216;0.0)	267509 (229403;380790)
5	-0.1	0.05	312431 (- 143469;- 2147483648)	-276354 (- 453405;-228199)	0.0 (- 1.219;0.0)	267440 (229403;380809)
5	-0.1	0.1	312935 (- 143240;- 2147483648)	-276667 (- 453692;-228398)	0.0 (- 1.223;0.0)	267374 (229403;380827)
5	0	0	312955 (- 141379;- 2147483648)	-278626 (- 456559;-229403)	0.0 (- 1.261;0.0)	266513 (229403;380110)
5	0	0.05	301586 (- 145043;- 2147483648)	-278740 (- 456835;-229403)	0.0 (- 1.264;0.0)	266426 (229403;380103)
5	0	0.1	301902 (- 144785;- 2147483648)	-278850 (- 457097;-229403)	0.0 (- 1.267;0.0)	266336 (229403;380095)
5	0.1	0	296658 (- 143052;- 2147483648)	-279614 (- 459631;-229403)	0.0 (- 1.318;0.0)	265626 (229403;380329)
5	0.1	0.05	297041 (- 142699;- 2147483648)	-279614 (- 459707;-229403)	0.0 (- 1.323;0.0)	265592 (229403;380375)
5	0.1	0.1	297610 (- 142370;- 2147483648)	-279614 (- 459779;-229403)	0.0 (- 1.328;0.0)	265556 (229403;380396)
5	0.2	0	305773 (- 138869;- 2147483648)	-279614 (- 462068;-229403)	0.0 (- 1.373;0.0)	265251 (229403;380989)
5	0.2	0.05	306263 (- 138108;- 2147483648)	-279614 (- 462412;-229403)	0.0 (- 1.377;0.0)	265248 (229403;381054)
5	0.2	0.1	306733 (- 137924;- 2147483648)	-279614 (- 462741;-229403)	0.0 (-1.38;0.0)	265245 (229403;381116)
5	0.3	0	296185 (- 141271;- 2147483648)	-279614 (- 465361;-229379)	0.0 (-1.41;0.0)	265066 (229403;381391)

5	0.3	0.05	296456 (-141035;-2147483648)	-279614 (-465472;-229360)	0.0 (-1.414;0.0)	265039 (229403;381437)
5	0.3	0.1	296647 (-140811;-2147483648)	-279614 (-465577;-229342)	0.0 (-1.418;0.0)	265013 (229403;381481)
5	0.82	0	287382 (-137089;-2147483648)	-279614 (-477472;-229403)	0.0 (-1.551;0.0)	262877 (229374;382923)
5	0.82	0.05	286035 (-137386;-2147483648)	-279614 (-477681;-229403)	0.0 (-1.553;0.0)	262877 (229354;382937)
5	0.82	0.1	286266 (-137225;-2147483648)	-279614 (-477880;-229403)	0.0 (-1.555;0.0)	262877 (229345;382949)
10	-0.5	0	331325 (-110302;-2147483648)	-271910 (-520757;-219184)	0.0 (-1.038;0.307)	295628 (229403;466475)
10	-0.5	0.05	327882 (-113245;-2147483648)	-272027 (-521338;-219251)	0.0 (-1.044;0.302)	295569 (229403;466505)
10	-0.5	0.1	328710 (-112631;-2147483648)	-272133 (-521893;-219316)	0.0 (-1.05;0.296)	295454 (229403;466534)
10	-0.4	0	322138 (-114173;-2147483648)	-274968 (-528942;-221327)	0.0 (-1.127;0.196)	292704 (229403;466808)
10	-0.4	0.05	319479 (-116564;-2147483648)	-275462 (-529312;-221356)	0.0 (-1.13;0.195)	292593 (229403;466793)
10	-0.4	0.1	319956 (-116191;-2147483648)	-275934 (-529665;-221433)	0.0 (-1.135;0.193)	292444 (229403;466778)
10	-0.3	0	293186 (-122265;-2147483648)	-279614 (-534853;-222380)	0.0 (-1.246;0.141)	288922 (229403;466738)
10	-0.3	0.05	293938 (-121983;-2147483648)	-279614 (-535334;-222371)	0.0 (-1.253;0.136)	288772 (229403;466768)
10	-0.3	0.1	294662 (-121715;-2147483648)	-279614 (-535771;-222362)	0.0 (-1.26;0.132)	288628 (229403;466795)
10	-0.2	0	304010 (-117442;-2147483648)	-279614 (-542881;-224284)	0.0 (-1.382;0.08)	285081 (229403;466778)
10	-0.2	0.05	303051 (-117788;-2147483648)	-279614 (-543347;-224485)	0.0 (-1.388;0.076)	284647 (229403;466766)
10	-0.2	0.1	304298 (-117523;-2147483648)	-279614 (-543747;-224678)	0.0 (-1.393;0.073)	284232 (229403;466755)
10	-0.1	0	273173 (-120297;-2147483648)	-279614 (-548826;-227168)	0.0 (-1.495;0.0)	281253 (229403;466543)
10	-0.1	0.05	273727 (-120081;-2147483648)	-279614 (-549431;-227366)	0.0 (-1.503;0.0)	281032 (229403;466508)
10	-0.1	0.1	274168 (-119875;-2147483648)	-279614 (-549938;-227556)	0.0 (-1.509;0.0)	280821 (229403;466475)
10	0	0	249523 (-118325;-2147483648)	-279614 (-555168;-228836)	0.0 (-1.619;0.0)	279661 (229403;464756)
10	0	0.05	249728 (-118011;-2147483648)	-279614 (-555585;-228917)	0.0 (-1.624;0.0)	279632 (229403;464830)
10	0	0.1	248872 (-118899;-2147483648)	-279614 (-555982;-228996)	0.0 (-1.629;0.0)	279614 (229403;464901)

10	0.1	0	245092 (-118855;-2147483648)	-279614 (-562241;-229403)	0.0 (-1.699;0.0)	279614 (229403;464310)
10	0.1	0.05	244511 (-120063;-2147483648)	-279614 (-562893;-229403)	0.0 (-1.706;0.0)	279614 (229403;464325)
10	0.1	0.1	244943 (-119699;-2147483648)	-279614 (-563408;-229403)	0.0 (-1.712;0.0)	279614 (229403;464325)
10	0.2	0	242770 (-118070;-2147483648)	-279614 (-566573;-229401)	0.0 (-1.804;0.0)	279614 (229403;463657)
10	0.2	0.05	242140 (-119736;-2147483648)	-279614 (-566742;-229403)	0.0 (-1.81;0.0)	279614 (229403;463724)
10	0.2	0.1	242401 (-119449;-2147483648)	-279614 (-566913;-229403)	0.0 (-1.815;0.0)	279614 (229403;463788)
10	0.3	0	240182 (-117772;-2147483648)	-279614 (-570464;-229403)	0.0 (-1.865;0.0)	279614 (229403;464187)
10	0.3	0.05	240481 (-117346;-2147483648)	-279614 (-570770;-229403)	0.0 (-1.87;0.0)	279614 (229403;464165)
10	0.3	0.1	240768 (-117138;-2147483648)	-279614 (-571036;-229403)	0.0 (-1.878;0.0)	279614 (229403;464143)
10	0.82	0	229615 (-110087;-2147483648)	-279614 (-589096;-229403)	0.0 (-2.198;0.0)	279614 (229403;460911)
10	0.82	0.05	229761 (-109921;-2147483648)	-279614 (-589487;-229403)	0.0 (-2.202;0.0)	279614 (229403;460825)
10	0.82	0.1	229902 (-109763;-2147483648)	-279614 (-589859;-229403)	0.0 (-2.207;0.0)	279614 (229403;460750)

**Table G1. Extended results table per 1000 patients.** An extended version of Table 2 in the manuscript. Results are presented as median with IQR, the baseline follow-up horizon of 5-year was used. For all scenarios, the optimal ICV threshold in was 110mL and the optimal MMR threshold was 1.4. Optimal thresholds were based on the maximum net monetary benefit at a willingness to pay of €80000. \*: Baseline EVT effect modification ORs were 0.98 (95%CI:0.881;1.091) for ICV and 1.010 (95%CI:0.994;1.560) for MMR. ICER: incremental cost effectiveness ratio. ICV: ischaemic core volume. MMR: core-penumbra mismatch ratio. EVT: endovascular treatment. OR: odds ratio. CTP: CT perfusion.

**Online supplement H. Effects in included sub-populations**

**Figure H1. Variations in outcome per data source.** The optimal ischemic core volume threshold of  $\geq 110$  mL was used to exclude patients for EVT. Regardless of the data source used, the conclusion was the same. For patients from the MR CLEAN NOIV data, included within 4.5 hours after symptom onset due to intravenous thrombolysis eligibility criteria for inclusion, the cost savings were more profound. This was attributed to a shorter survival (and less costs) of patients with a relatively good baseline 90-day mRS outcome if patients were excluded for EVT.



**Supplementary material references**