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Original research

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jnnp-2023-331862).

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Received 17 May 2023
Accepted 19 November 2023
Published Online First 18 December 2023

To cite: van Voorst H, Hoving JW, Koopman MS, *et al*. *J Neurol Neurosurg Psychiatry* 2024;**95**:515–527.

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 (ΔCosts) and quality-adjusted life years (ΔQALY) 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≥110 mL) or core-penumbra mismatch ratio (MMR≤1.4) thresholds resulted in losses of health (median ΔQALYs for ICV≥110 mL: −3.3 (IQR: −5.9 to −1.1), for MMR≤1.4: 0.0 (IQR: −1.3 to 0.0)) with median ΔCosts for ICV≥110 mL of −€348 966 (IQR: −€712 406 to −€51 158) and for MMR≤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 ≥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≥110 mL) or core-penumbra mismatch ratio (MMR≤1.4) thresholds, resulted in a loss of health (median Δquality-adjusted life years for ICV≥110 mL: −3.3 (IQR: −5.9 to −1.1), for MMR≤1.4: 0.0 (IQR: −1.3 to 0.0)) with median ΔCosts for ICV≥110 mL of −€348 966 (IQR: −€712 406 to −€51 158) and for MMR≤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).[1] 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.[1] 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.[2–4] 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.[5] 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,[6] no statistically significant decay of EVT effect related to these CTP measures was observed in a pooled analysis of five landmark EVT trials.[1] Additional post hoc analyses identified a reduction in EVT benefit depending on ICV in patients aged ≥75 years.[7] As a result, discrepancies exist between European and North American guidelines and CTP is still frequently considered to guide patient selection for EVT.[8–10] Since recent large stroke trials had restrictive inclusion criteria, varying imaging protocols, and only evaluated patient outcome at 90 days follow-up,[2–4] 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.[11–13] 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.[1 6] Namely, the EVT effect could be lower in patients with a large infarct or in elderly subgroups.[7] 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.[14] 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.[11–13]

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.[15] 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.[8] 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,[6 16] and treatment effect modification due to CTP measures[1] 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),[17] MR CLEAN-MED (ISRCTN76741621),[18] the MR CLEAN Registry,[19] 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.[15] Online supplemental B describes minor changes to the protocol.[15] CTP acquisition, post-processing and quality assessment are presented in detail in online supplemental C.[15] 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.[20] 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[21] and death[22] inflated with patient-specific HRs.[23] Simulations and analyses were performed with publicly available custom-developed Python software (github.

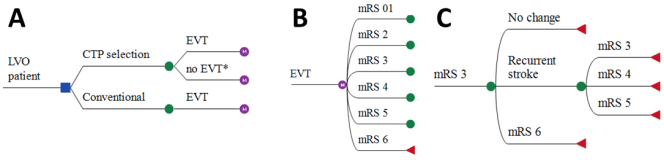

Figure 1 Markov model structure. (A) Patients with a confirmed large vessel occlusion (LVO) who were eligible for endovascular treatment (EVT) were simulated. Each patient was simulated as if NCCT and CTA imaging was used with or without additional CT perfusion (CTP) for selection of patients for EVT. 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[20] and predefined in our protocol.[15] 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.[24] Historical and forecasted inflation rates for healthcare costs were used to adjust the costs over time.[25 26]

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 (ΔCosts) and ΔQALYs between the simulated CTP and no CTP arms.

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

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

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 ≥70 mL for ICV and ≤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 ΔCosts and ΔQALYs 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)).[16] 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 ≤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.[6] 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).[1] 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,[1 27] 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 ≥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≥70 mL, 23/703 (3.3%) patients with an ICV≥110 mL, 19/703 (2.7%) patients with an MMR≤1.8 and 5/703 (0.7%) patients with an MMR≤1.4.

Baseline model and one-way sensitivity

In the baseline simulations, excluding patients with an ICV≥70 mL for EVT resulted in losses of health (ΔQALY: −33.8), higher costs (Δcosts: €385 866), an ICER of −11 432 and NMB of −€3 086 208 per 1000 patients. Excluding patients with an MMR≤1.8 for EVT resulted in losses of health (ΔQALY: −5.8), higher costs (Δcosts: €54 836), an ICER of −9834 and NMB of −€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,

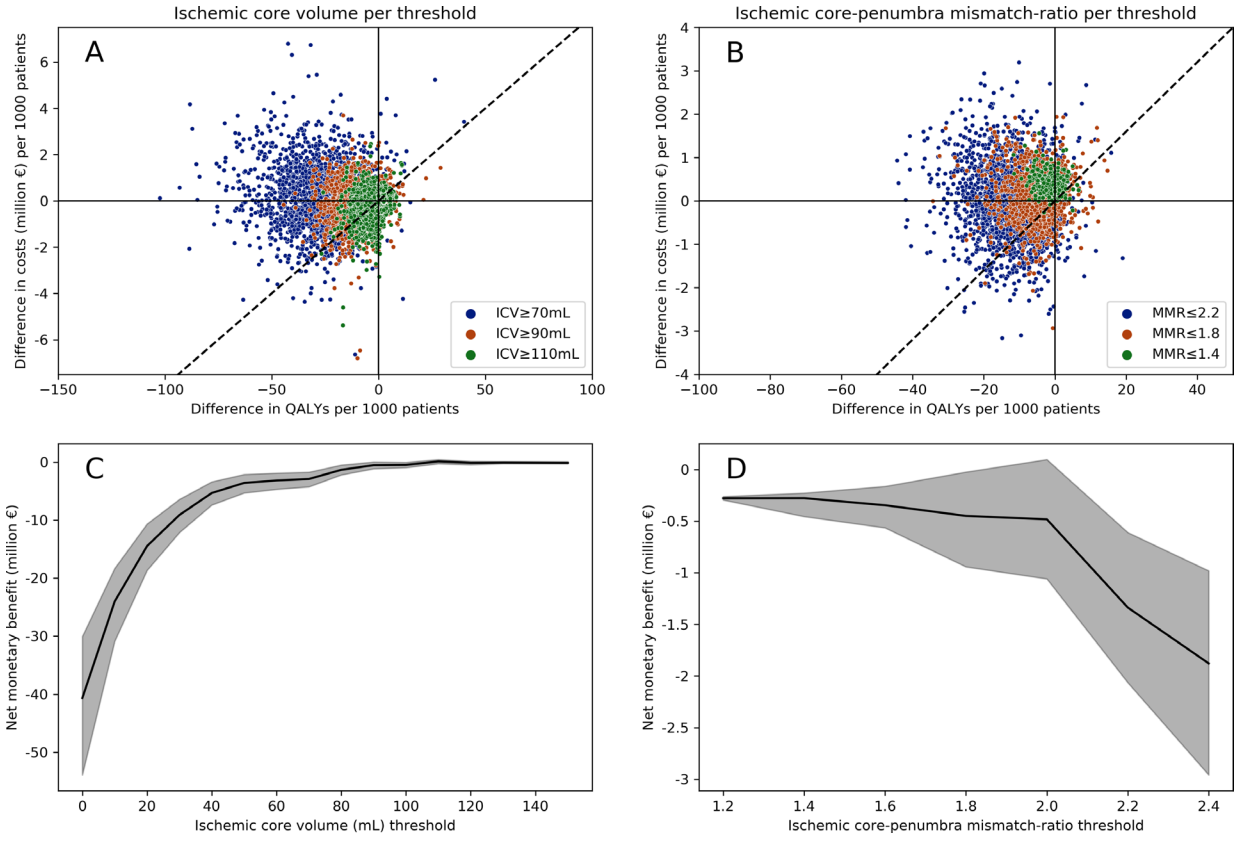

Figure 2 Probabilistic sensitivity analyses results. (4A–B) Each point in the scatter plot is a cohort of patients that was simulated twice; one time as if the optimal CTP measure (CTP arm) was used to exclude patients for EVT and one time as if all patients received EVT (no CTP arm). The x and y coordinates 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 10mL 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 ≥110mL. (4D) Similar to 4C but considers the MMR, the optimal threshold was ≤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 ICV≥110 mL and MMR≤1.4. Using ICV≥110 mL to exclude patients for EVT resulted in losses of health (ΔQALYs 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 (ΔCosts 5-year median: −€348 966 (IQR: −€712 406 to −€51 158), 10-year median: −€246 679 (IQR: −€733 714 to €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: €102 227 (IQR: −€282 942 to €431 923), 10-year median: −€97 781 (IQR: −€644 889 to €420 136)) per 1000 patients. Using MMR≤1.4 to exclude patients for EVT resulted in limited to no losses of health (ΔQALYs 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 (ΔCosts 5-year follow-up median: €266 513 (IQR:€229 403 to €380 110), 10-year follow-up median: €279 661 (IQR: €229 403 to €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: −€278 626 (IQR: −€456 559 to −€229 403), 10-year follow-up median: −€279 614 (IQR: −€555 168 to −€228 836)) per 1000 patients. Due to the limited number of patients with an ICV above (≥110 mL) and MMR below (≤1.4) the optimal decision threshold for EVT patient exclusion, the ΔQALY 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

			Net monetary benefit (NMB) in € per 1000 patients				
			EVT effect OR				
CTP measure and optimised threshold	Follow-up horizon (years)	Effect modification due to ICV or MMR (OR)	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)	2.49 (95% CI: 2.03 to 3.12)‡
ICV≥110 mL	5	**0.98 (95% CI: 0.881 to 1.091)***	75 260 (−256 606 to 356 220)	92 540 (−274 492 to 387 168)	102 227 (−282 942 to 431 923)	115 014 (−282 947 to 472 304)	126 436 (−294 179 to 516 591)
	5	**0.93 (95% CI: 0.831 to 1.041)**	52 532 (−158 294 to 247 178)	58 740 (−171 751 to 270 871)	71 360 (−189 586 to 298 635)	81 540 (−202 099 to 334 318)	95 139 (−235 410 to 378 627)
	5	**0.88 (95% CI: 0.781 to 0.991)**	44 361 (−84 207 to 180 651)	45 137 (−97 373 to 189 920)	52 380 (−117 014 to 211 993)	57 805 (−131 228 to 233 197)	69 596 (−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 (−433 414 to −222 141)	−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 (−433 887 to −222 227)	−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)
	10	**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[9] and the study by Campbell *et al* for ICV-based effect modification.[4]
†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.[1] 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.

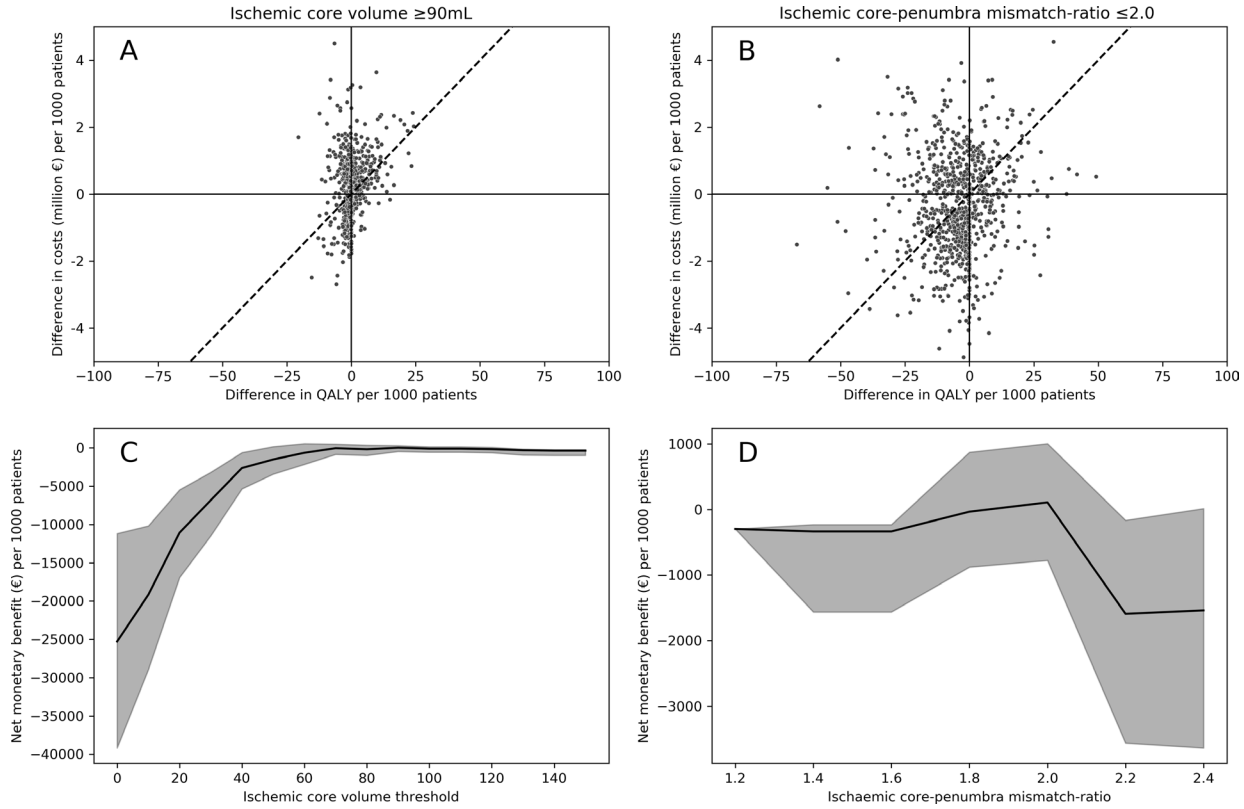

Figure 3 ICER plot for CTP-based EVT selection in an elderly population. For this simulation a follow-up horizon of 10 years, 0.3 decrease of the EVT effect (OR: 1.37 (95% CI: 0.91 to 2.0)), and a 0.1 decrease of the ICV or MMR based EVT effect modification (OR: 0.88 (95% CI: 0.781 to 0.991)) were used to simulate cohorts with patients aged ≥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 ≥90mL for excluding patients for EVT. (5B) PSA performed for MMR with an optimal threshold of ≤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 ΔQALY 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, ΔCosts and ΔQALYs. 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 MMR≤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 ≥80 years resulted in a less profound losses of QALYs (ΔQALYs ICV median: 0.0 (IQR: −0.8 to 0.5), MMR median: −1.2 (IQR: −8.8 to 0.0)) and additional costs (ΔCosts ICV median: €34 920 (IQR: −€293 371 to €524 269), MMR median: −€229 448 (IQR: −€1 178 568 to €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: −€461 957 to €305 633), MMR median: €108 270 (IQR: −€775 446 to €1 004 928)) per 1000 patients included zero. These results achieved optimal NMBs for an ICV≥90 mL and MMR≤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 ≥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.[2 3] 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.[28] 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.[1] Finally, in the most favourable CTP-based EVT patient selection scenario, we considered a lower EVT effect for patients aged ≥80 years. However, current evidence suggests a higher EVT effect for patients aged ≥85 years while we used a reduced EVT effect.[29] Other research suggests that patients aged ≥75 years with ICV≥50 or ≥85 mL might have a lower EVT effect.[7]

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.[6 30] 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.[31 32] 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.[33] However, as represented by the baseline characteristics in this study, this combination of highly unfavourable baseline characteristics is rare in our AIS population.[7] Furthermore, long-term follow-up studies and cost-effectiveness analyses of the large infarct RCTs will provide a higher level of evidence.[2–4]

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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Funding The CLEOPATRA healthcare evaluation study was funded by Leading the Change (LtC). LtC is financed by Zorgverzekeraars Nederland (ZN) and supports various healthcare evaluations in the Netherlands as part of the 'Healthcare Evaluation Netherlands' project. LtC was not involved in the study design, monitoring, data collection, statistical analyses, interpretation of results or manuscript writing, but the progress of the study was continuously monitored by LtC. The MR CLEAN-NO IV trial (ISRCTN80619088) and MR CLEAN-MED trial (ISRCTN76741621) were part of the Collaboration for New Treatments of Acute Stroke (CONTRAST) consortium. The CONTRAST consortium acknowledges the support from the Netherlands Cardiovascular Research Initiative, an initiative of the Dutch Heart Foundation (CVON2015-01: CONTRAST), and from the Brain Foundation Netherlands (HA2015.01.06). The collaboration project is additionally financed by the Ministry of Economic Affairs by means of the PPP Allowance made available by the Top Sector Life Sciences & Health to stimulate public–private partnerships (LSHM17016). This work was funded in part through unrestricted funding by Stryker, Medtronic and Cerenovus. The funding sources were not involved in study design, monitoring, data collection, statistical analyses, interpretation of results or manuscript writing.

Competing interests BJE reports grants from LtC (ZonMW and TKI-PPP of Health Holland). WHvZ reports speaker fees from Cerenovus, NicoLab and Stryker, and consulting fees from Philips, all paid to Institution. DWJD report grants from the Dutch Heart Foundation, Brain Foundation Netherlands, ZON MW, Stryker, Medtronic, Cerenovus, Thrombolytic Science, received by the Erasmus University Medical Center outside this project. AJY reports Research grants from Medtronic, Cerenovus, Penumbra, Stryker, and Genentech. Consultant for Penumbra, Cerenovus, Nicolab, Philips, Vesalio, Zoll Circulation, and NIH/NINDS. CBM: grants from Healthcare Evaluation Netherlands, CVON/Dutch Heart Foundation, TWIN foundation and Stryker during the conduct of the study and from European Commission outside this project (all paid to institution) and is shareholder of Nicolab. All other contributors report no other conflicts of interest.

Patient consent for publication Not applicable.

Ethics approval Amsterdam UMC ethical review board and Erasmus MC ethical review board. Patient inclusion was in adherence with the declaration of Helsinki and was subject to an ethical board review. The CLEOPATRA study protocol has been reviewed by the Amsterdam UMC ethical review board and was waived for informed consent (Amsterdam UMC reference: W19_281#19.334). Retrospective, large scale, observational studies do not fall under the Medical Research Involving Human Subjects Act (WMO). For patients included in the MR CLEAN-NO IV (ISRCTN80619088, registered 31 October 2017), and MR CLEAN MED (ISRCTN76741621, registered 7 December 2017) trials informed consent has been received previously. The ethical review board of the Erasmus MC has waived the requirement for informed consent for patients included in the MR CLEAN Registry (internal reference Erasmus MC: MEC-2014-235, 27 August 2014). Patient inclusion was in adherence with the declaration of Helsinki and was subject to an ethical board review. The CLEOPATRA study protocol has been reviewed by the Amsterdam UMC ethical review board and was waived for informed consent (Amsterdam UMC reference: W19_281#19.334). Retrospective, large scale, observational studies do not fall under the Medical Research Involving Human Subjects Act (WMO). For patients included in the MR CLEAN-NO IV (ISRCTN80619088, registered 31 October 2017), and MR CLEAN MED (ISRCTN76741621, registered 7 December 2017) trials informed consent has been received previously. The ethical review board of the Erasmus MC has waived the requirement for informed consent for patients included in the MR CLEAN Registry (internal reference Erasmus MC: MEC-2014-235, 27 August 2014).

Provenance and peer review Not commissioned; externally peer reviewed.

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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