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Stroke

CLINICAL AND POPULATION SCIENCES

Economic Evaluation of Endovascular Treatment for Acute Ischemic Stroke

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BACKGROUND AND PURPOSE: Endovascular treatment for acute ischemic stroke has been proven clinically effective, but evidence of the cost-effectiveness based on real-world data is scarce. The aim of this study was to assess whether endovascular therapy plus usual care is cost-effective in comparison to usual care alone in acute ischemic stroke patients.

METHODS: An economic evaluation was performed from a societal perspective with a 2-year time horizon. Empirical data on health outcomes and the use of resources following endovascular treatment were gathered parallel to the MR CLEAN trial (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) and its 2-year follow-up study. Incremental cost-effectiveness ratios were calculated as the extra costs per additional patient with functional independence (modified Rankin Scale score 0–2) and the extra cost per quality-adjusted life year gained.

RESULTS: The mean costs per patient in the intervention group were $126 494 versus $143 331 in the control group (mean difference, −$16 839 [95% CI, −$38 113 to $5456]). Compared with patients in the control group, more patients in the intervention group achieved functional independence, 37.2% versus 23.9% (absolute difference, 13.3% [95% CI, 4.0%–22.0%]) and they generated more quality-adjusted life years, 0.99 versus 0.83 (mean difference of 0.16 [95% CI, 0.04–0.29]). Endovascular treatment dominated standard treatment with $18 233 saved per extra patient with a good outcome and $105 869 saved per additional quality-adjusted life year.

CONCLUSIONS: Endovascular treatment added to usual care is clinically effective, and cost saving in comparison to usual care alone in patients with acute ischemic stroke.

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Key Words: cost savings ■ follow-up studies ■ ischemic stroke ■ quality-adjusted life years

Stroke is the third major cause of death and the most important cause of disability worldwide.[1] The disease poses a heavy burden for both the affected patient as well as society. In the Netherlands, annual health care costs in 2011 for patients with a stroke were ≈1.84 billion euros (EUR).[2] In comparison, in the United Kingdom, the treatment and productivity loss arising from stroke results in total societal costs of 8.9 billion pounds a year,

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†A list of all MR CLEAN investigators is given in the Appendix.
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Nonstandard Abbreviations and Acronyms

ICER	incremental cost-effectiveness ratios
IVT	intravenous thrombolysis
MR CLEAN	Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands
mRS	modified Rankin Scale
QALY	quality-adjusted life year
THRACE	Thrombectomie des Artères Cerébrales

whereas in the United States, the estimated direct and indirect costs related to stroke patients in 2010 were 73.7 billion US dollars (USD).[3,4]

Treatment of acute ischemic stroke is aiming at early vessel recanalization to restore blood flow. Early vessel recanalization strongly correlates with improved clinical outcome and reduced mortality.[5,6] Endovascular treatment has been proven more effective to achieve early vessel recanalization, which resulted in better short- and long-term clinical outcomes compared with standard treatment strategies, including intravenous thrombolysis (IVT) with recombinant tissue-type plasminogen activator.[7,8] Hence, endovascular treatment is now regarded standard care for stroke patient and has been adopted in international guidelines. Despite its convincing clinical efficacy, large-scale implementation is often hampered by the relatively high costs involved with this treatment. Regulatory offices and health care insurance organizations in several countries demand cost-effectiveness studies to be done and to show a beneficial effect within certain cost limits before reimbursement is granted. Although endovascular treatment is an expensive treatment modality, it may well be cost-effective in comparison to the standard treatment by improving longer-term survival and quality of life and by reducing demands for rehabilitation and nursing home stay after hospital discharge.[9–12] To date, evidence of the cost-effectiveness of endovascular treatment for acute ischemic stroke based on real-world data is scarce.[13–16] The aim of the current study is to assess whether endovascular therapy plus usual care is cost-effective in comparison to usual care alone in patients with acute ischemic stroke.

METHODS

Study Design and Patient Population

This economic evaluation was conducted parallel to the MR CLEAN trial (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) and the 2-year follow-up study of the original trial. The study design, methods, and results of MR CLEAN and its 2-year follow-up study have been published previously.[8,17–19]

The study is reported according to the Consolidated Health Economic Evaluation Reporting Standards guideline.[20] A completed checklist is presented as Data Supplement. The clinical and economic data of this study are available from the corresponding author upon reasonable request.

In brief, MR CLEAN was a randomized, multicenter trial comparing endovascular treatment plus usual care (intervention group) to usual care alone (control group) in patients with acute ischemic stroke caused by a proximal intracranial arterial occlusion of the anterior circulation. Usual care included best medical management according to national and international guidelines, including IVT. Trial treatment was open-label, and the evaluation of outcomes was blinded. Endovascular treatment consisted of intraarterial catheterization with a microcatheter to the level of occlusion and delivery of a thrombolytic agent, mechanical thrombectomy, or both.

In total, 500 patients from 16 medical centers in the Netherlands were randomly assigned between December 2010 and April 2014, of which 233 to intervention plus usual care and 267 patients to usual care alone. The mean age was 65 years (range 23–96 years), and 445 patients (89.0%) were treated with IVT before randomization. Actual endovascular treatment was performed in 196 of the 233 patients in the intervention group, and 190 (81.5%) of these were treated with retrievable stents.[18] At 2-year follow-up, primary outcome (modified Rankin Scale [mRS]) score was available in 391 of the 500 patients.[8]

Perspective and Time Horizon

Endovascular treatment of acute ischemic stroke was evaluated economically from a societal perspective, including the costs of health care as well as nonreimbursed out-of-pocket expenses by patients. The time horizon was 2 years, in accordance with the length of the long-term clinical follow-up.

Measurements and Valuation of Costs and Effects

Four information sources were used to gather data on health care resources: case report forms, medical files, hospital information systems, and the Erasmus University/Institute of Medical Technology Assessment Medical Consumption Questionnaire—adapted to the study setting—during follow-up at 3 months, 6 months, 1 year, 18 months, and 2 years following randomization. Unit costing of health care resources was done in adherence to the most recent Dutch manual for costing in health care research by the Erasmus Institute of Medical Technology Assessment in collaboration with the National Health Care Institute.[21]

The original study was conducted in EUR with the base year 2014. If unit costs originated from another year, we applied general consumer price indexing (Table I in the Data Supplement). For conversion to USD, we used the average exchange rate EUR/USD of January 1, 2014 (1.3764). Unit costs of endovascular treatment were determined by detailed calculation of personnel, materials, and overhead. See the Data Supplement for a detailed description of the gathered resources, unit costing, and calculation of costs during the follow-up period.

Health effects were assessed with the use of the mRS score for the patient's functional outcome and EuroQol EQ-5D-3L questionnaire for the patient's quality of life at 3 months, 6

months, 1 year, 18 months, and 2 years. The mRS score is an ordinal scale, ranging from 0 (no disability) to 6 (death). Scores of 0 to 2 represent functional independence (good outcome), and scores of 3 to 6 represent functional dependence or death (poor outcome).[22,23] The EQ-5D-3L is a descriptive system existing of 5 domains: mobility, self-care, usual activities, and pain/discomfort and anxiety/depression. Each dimension has 3 levels: (1) no problems; (2) some problems; and (3) extreme problems. We transposed each EQ-5D-3L health status profile during follow-up into a health utility score by applying an existing scoring algorithm for the Netherlands, based on preferences from the general public, that were elicited with the time trade-off valuation technique.[24] Health utilities scores range from −0.329 for worst conditions to 1.0 for the best health status, with the health utility of death set to zero. The mRS score was assessed by telephone by 2 experienced study investigators; one assessed the 3-month mRS sore, and one assessed the mRS score during the rest of the follow-up. In addition, the patient or his/her primary caregiver was invited to complete the EuroQol EQ-5D-3L questionnaire.

Quality-adjusted life years (QALY) were calculated by taking the sumproduct of the derived health utilities and the lengths of the preceding periods between measurements or measurement and baseline.

To account for time preference, discounting was done for the second year of follow-up, at a rate of 4% for costs, and a rate of 1.5% for QALYs, both in agreement with the above-mentioned Dutch manual for costing in health care research.[25]

Primary outcomes were the difference in costs between the treatment arms per patient reaching functional independence (mRS score 0–2) and per QALY.

Standard Protocol Approvals, Registrations, and Patient Consents

All patients or their legal representatives provided written informed consent before randomization in the trial. A central medical ethics committee and the research board of each participating center approved the study protocol. The study sponsors were not involved in the study design, study conduct, protocol review, or article preparation or review. The MR CLEAN is registered under number 1804 in the Dutch trial register and under ISRCTN10888758 in the ISRCTN register.

Statistical Analyses

Differences between the intervention and control groups concerning the use of resources, costs and QALYs were calculated along with their 95% (bias-corrected and accelerated) CIs (detailed description of the calculated CIs is provided in the Data Supplement). Incremental cost-effectiveness ratios (ICERs) were calculated as the extra costs per additional patient with good functional outcome (mRS score 0–2) and the extra cost per QALY gained. Results for the ICER of the extra costs per QALY gained are graphically displayed by planes with cost differences on the *y*-axis and QALY differences on the *x*-axis (cost/effectiveness-plane) after nonparametric bootstrapping by drawing 1000 samples of the same size as the original samples with replacement.

All analyses were performed with the use of SPSS software (version 24.0).

Missing Data

We handled missing patient data during the 2 years of follow-up by making use of last observation carried forward and backward and model-based multiple imputation. A detailed description of the methods and analyses of missing data can be found in the Data Supplement. The ICER of the extra costs per additional patient with a good functional outcome (mRS score 0–2) was calculated only for patients who completed the follow-up at 2 years (n=391) without multiple imputation for missing data; under this restriction the cost-effectiveness analysis closely mimics the clinical analysis of the dichotomized primary outcome.[8]

Sensitivity Analyses

Both undiscounted and discounted results are reported. Furthermore, 2 alternatives for the multiple imputation approach of missing data were explored, applied to regular inpatient hospital days and intensive care unit-days analyses. First, missing data were ignored by only using the available data. Second, a Kaplan-Meier survival analysis approach to the cost domain rather than the time domain was done with censoring of patients known to have missing data. Results of the different approaches can be found in Table IV in the Data Supplement.

RESULTS

Used Resources and Costs

Table 1 shows the mean difference between the intervention and control group regarding the use of resources during the 2 years of follow-up. The numbers of inpatient days and day care treatments in a rehabilitation center and the number of consultations of a physiotherapist were lower in the intervention group.

Table 2 shows the mean difference between the intervention and control group in health care costs and out-of-pocket expenses during the 2 years of follow-up. The undiscounted mean costs of the intervention (mean difference, $12 612 [95% CI, $12 199–$13 074]) and other diagnostic and therapeutic procedures ($314 [95% CI, $15–$614]) were higher in the intervention group. However, the lower use of resources for inpatient (−$10 958 [95% CI, −$19 753 to −$2164]) and day care treatment (−$4802 [95% CI, −$8024 to −$1580]) in a rehabilitation center and for consultations of the physiotherapist (−$818 [95% CI, −$1455 to −$180]) resulted in undiscounted mean costs savings in favor of the intervention group.

From a societal perspective, endovascular treatment generated mean costs of $126 494 (95% CI, $113 962–$140 320) versus $143 331 (95% CI, $130 509–$155 558) in the control group, with a mean difference of −$16 839 (95% CI, −$38 113 to $5456, *P*=0.073) per patient.

In the group of 391 patients who completed the 2 years of follow-up, the undiscounted mean societal costs per patient were $102 198 (95% CI,

Table 1. Mean Difference Between Treatment Groups in Resource Use During 2 Years of Follow-Up, Including Lower and Upper Limits of the 95% CI

	Intervention (n=233)	Control (n=267)	Mean difference	Lower 95%	Upper 95%
Acute interventions					
Endovascular procedure, total (%)*	216 (92.7%)	1 (0.4%)			
IVT, total (%)	203 (87.1%)	242 (90.6%)			
Hospital admission, d					
Regular admission	15.30	16.65	−1.39	−3.64	0.87
ICU admission	1.03	1.60	−0.56	−1.25	0.12
Institutional care, d					
Rehabilitation center	61.04	78.35	−17.31	−31.20	−3.42
Day care rehabilitation center	13.78	25.18	−11.40	−19.05	−3.75
Nursing home	100.53	124.24	−23.70	−56.84	9.44
Home care, h					
Help	90.65	128.27	−37.62	−79.02	3.78
Care	151.14	173.28	−22.14	−83.38	39.09
Nursing	76.33	95.26	−18.93	−55.06	17.20
Consultations (visits)					
General practitioner	7.78	6.61	1.18	−0.55	2.91
Neurologist	2.60	2.72	−0.12	−0.94	0.70
Physiotherapist	48.78	66.78	−18.00	−32.02	−3.97
Ergo therapist	15.83	20.25	−4.42	−11.69	2.86
Speech therapist	19.19	27.92	−8.73	−18.15	0.69

ICU indicates intensive care unit; and IVT, intravenous thrombolysis.

*In the intervention arm 17 patients eventually did not receive endovascular treatment. These patients were not charged with procedural costs of the endovascular treatment. Furthermore, in 3 patients in the intervention arm, endovascular therapy was initiated, however, the procedure was terminated before actual thrombectomy could have taken place. In the control arm, one patient crossed over to the intervention arm and received endovascular treatment. These patients were charged with procedural costs of endovascular treatment.

$90 563–$114 994) in the intervention group and $104 616 (95% CI, $91 474–$117 904) in the control group, with a mean difference of −$2417 (95% CI, −$21 956 to $18 408 *P*=0.812) per patient.

Results of the discounted costs are presented in the Data Supplement and were similar to the undiscounted costs (Table III in the Data Supplement).

Health Effects

During the 2 years of follow-up, patients in the intervention group generated 0.99 (95% CI, 0.89–1.09) QALYs against 0.83 (95% CI, 0.75–0.91) in the control group, with a mean difference of 0.16 QALYs (95% CI, 0.04–0.29, *P*=0.01).

In the group of 391 patients with available mRS scores at 2 years, there was an absolute difference of 13.3 % (95% CI, 4.0–22.0) in the proportion of patients who were functionally independent (mRS score 0–2) in favor of the intervention; patients in the intervention group generated on average 0.92 QALYs (95% CI, 0.82–1.04) during the 2 years of follow-up, patients in the control group 0.73 QALYs (95% CI, 0.62–0.82), with a mean difference of 0.2 QALYs (95% CI, 0.06–0.36, *P*=0.01) in favor of the intervention group, which well coincided with the difference in good outcome.

Results of the discounted QALYs are presented in the Data Supplement and were similar to the undiscounted results.

Extra Costs per Patient With Good Functional Outcome

In the group of 391 patients, one extra patient recovered from the index stroke and became functionally independent for every 7 to 8 patients treated with endovascular treatment. The associated point-estimate for the incremental societal costs per patient with a good outcome was −$18 233, favoring the intervention.

Extra Costs per Additional QALY

The incremental costs per QALY gained were −$105 869, suggesting dominance—lower costs and better health outcomes—of the intervention over the control treatment. The Figure shows the cost/effectiveness-plane for the undiscounted mean differences between the intervention and control groups in societal costs and QALYs after 1000 bootstrap replications. Most replications, 97%, generated cost savings and QALY gains (the lower right quadrant), indicating that endovascular treatment has a probability of being cost-effective of at least 0.97.

Table 2. Mean Difference Between Treatment Groups in Undiscounted Costs During 2 Years of Follow-Up, Including Lower and Upper Limits of the 95% CI (in US Dollars)

	Intervention (n=233)	Control (n=267)	Mean difference	Lower 95%	Upper 95%
Acute interventions					
Endovascular procedure	12663	51	12612	12199	13074
IVT*	1140	1186	−45	−26	118
Hospital admission					
Regular admission	10004	10912	−895	−2385	568
ICU admission	1683	2604	−921	−2045	204
Other procedures (diagnostic and interventions)	2241	1924	314	15	614
Institutional care					
Rehabilitation center	38649	49607	−10958	−19753	−2164
Day care rehabilitation center†	5804	10607	−4802	−8024	−1580
Nursing home	23246	28727	−5481	−13145	2182
Home care					
Help	2495	3530	−1035	−2175	105
Care	10401	11925	−1524	−5738	2691
Nursing	7669	9571	−1902	−5532	1729
Consultations					
General practitioner	445	377	67	−32	167
Neurologist	354	370	−17	−128	95
Physiotherapist	2216	3034	−818	−1455	−180
Ergo therapist	720	919	−201	−531	129
Speech therapist	793	1153	−361	−750	29
Out-of-pocket expenses					
Transport	1997	2138	−140	−779	497
Informal care/private help	1862	1664	198	−483	880
OTC	1331	1226	105	−390	599

ICU indicates intensive care unit; IVT, intravenous thrombolysis; and OTC, over-the-counter medication.

*The costs of IVT with alteplase are based on the costs of alteplase per 50 mg; Alteplase comes in flacons of 50 mg. As most patients need > 50 mg with a maximum of 90 mg, each patient receiving intravenous alteplase was assigned as receiving 2 flacons, for a total of $1309.

†According to the Dutch cost manual for health care research-2015 one hour of treatment in a rehabilitation center in day care setting costs $ 211, based on paragraph 4.16 of the cost manual we assume 1 visit lasts 2 h (mean) for adults.

DISCUSSION

This economic evaluation shows that endovascular treatment is cost-effective after 2 years in comparison to the current standard treatment in patients with acute ischemic stroke of the anterior circulation. Functional health improvements on the mRS following endovascular treatment positively affect patients' quality of life. The initial investment of a rather expensive add-on treatment of almost $14000 rapidly pays off in reduced costs of rehabilitation (both inpatient stays as well as day care treatment), reduced costs of physiotherapy and, to a lesser extent, reduced costs of nursing home stay. In the total study population, we observed that the number of QALYs per patient in the first 2 years following stroke added up to about one single QALY on average; moreover, most patients in the group with complete follow-up were functionally dependent or died at the end of the 2 years (69.6% [272/391]). This signifies stroke as a disease with a heavy burden and the societal willingness to pay per QALY should be at the higher end of around $30000 to $100000 range of the European political benchmark. If so, the probability of endovascular treatment for stroke being cost-effective is almost one, with a net monetary benefit (as $100000 times the QALY difference and minus the cost difference) of $32466 (95% CI, $12114–$52399; undiscounted).

Strengths and Weaknesses

The current study is not directly comparable to any of the previous studies on this topic for several reasons. Most previously published studies were model-based for the longer-term follow-up, with the use of Markov modeling.[26–28] Input data in these studies were retrieved from different sources including available data from the literature or even expert opinion. Due to the different input data and methodology of the model-based studies, and subsequently the major uncertainty in the models and outcomes, it seems valid to compare our results to

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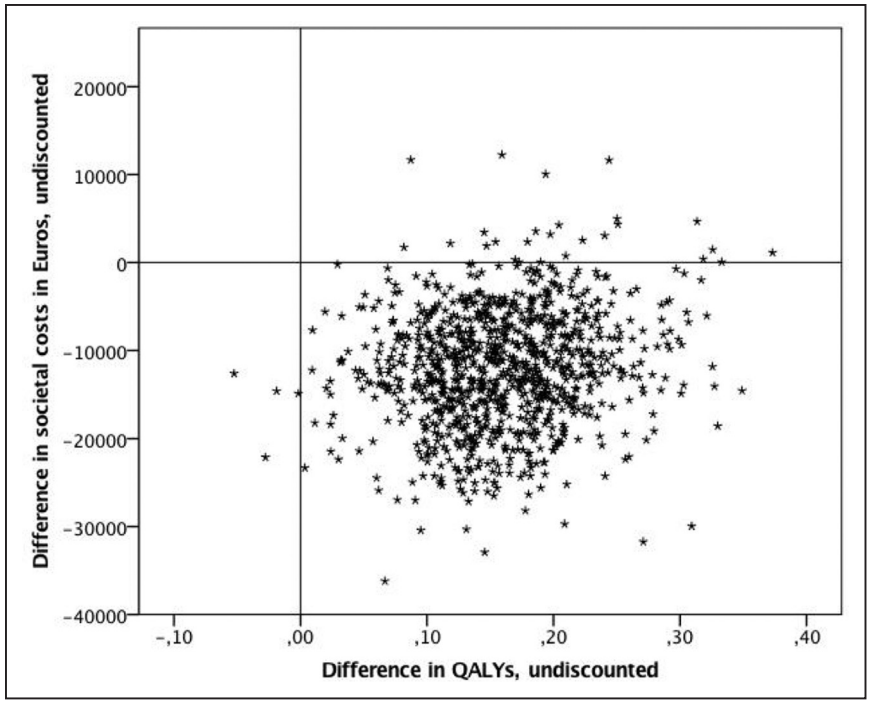

Figure. Undiscounted mean differences between intervention and control groups in societal costs (*y* axis) by quality-adjusted life years (QALYs; *x* axis) after 1000 bootstrap replications, costs are expressed in 2014 euros (equivalent of −55 056 United States dollar to 27 528 United States dollar on the *y* axis).

economic studies using empirical data alongside a randomized clinical trial.[13]

The THRACE study (Thrombectomie des Artères Cerébrales) group conducted such an economic evaluation alongside their THRACE trial. THRACE compared clinical outcomes at 3 months for patients with moderate to severe strokes who received either IVT alone or IVT and endovascular treatment, within 4 and 5 hours, respectively.[13] In total 414 patients were included. Individual-level cost and health utility data were collected from the perspective of the National Health Insurance system in France, which included only costs associated with the initial hospital stay. Their primary health-related outcomes were rate of functional independence at 3 months and the EQ-5D at 1 year. The ICER, corresponding to the cost of one additional averted disability case, was estimated at $19 379 (90% CI, $10 576–$79 822), whereas the ICER per one QALY gained was $14 881 (90% CI, $8595–$47 007).[13]

There are several important differences comparing THRACE trial to our study, all related to the clinical trial design as well as to the economic evaluation itself. THRACE compared the combination of endovascular treatment and IVT to IVT alone, THRACE included only a selected population based on stroke severity and THRACE had a limited duration of follow-up. In MR CLEAN in– and exclusion criteria were broad, reflecting every day clinical practice, and follow-up was available over a longer, 2-year period. The THRACE economic substudy included the initial procedural and hospitalization stay costs only. Thereby the high costs associated with rehabilitation and nursing home stay were not taking into account. As seen in our study, costs saved in these areas play an important part in the difference in costs between the treatment strategies, and subsequently in endovascular treatment showing near dominance over control. Therefore, results from THRACE will mainly inform negotiations between insurer and health care provider, whereas the societal perspective in our study has wider implications related to priority setting across health care settings.

Our economic evaluation has several limitations and particularities. First, the delayed start of the present study compared with the original trial starting date posed a methodological challenge with regard to the handling of missing data. We have chosen to use a multiple imputation approach as our main analysis. It resulted in intermediate estimates and differences, which presented the best, unbiased estimate available (see the illustration with the costs of inpatient hospital stay at the regular ward and intensive care unit in the Data Supplement, Table IV in the Data Supplement).

Second, we did not include costs associated with productivity loss by absenteeism from work or impaired productivity while at work in our study, also known as indirect costs, although usually included in economic evaluations from a societal perspective. In our study design, we did plan to perform a subgroup analysis of patients who would be an active member on the workforce. Because of its potential redundancy, the costs of productivity loss have not yet been addressed. Due to the delayed start of the long-term extension study with its multiple missing data together with an a priori limited size of this subgroup sincerely limits the information value of such an exercise. The convincing evidence of endovascular therapy as an efficient treatment modality emerging from the present economic evaluation suggests that extending the current

scope to the employer perspective would only further underpin the necessity of implementing this therapy as soon as possible.

Conclusions and Policy Implications

In many Western countries, patients with stroke depend on and have access to institutional care by the hospital, rehabilitation center and nursing home, and to noninstitutional care by physiotherapists and speech therapists. Therefore, the near dominance economically of the endovascular treatment over standard treatment with a high probability of cost savings per additional patient whose health has been improved, as demonstrated in our study, is highly relevant to other countries in the Western hemisphere that have at least a (roughly) comparable organization and financing of institutional and noninstitutional health care.

In conclusion, our study demonstrates that endovascular treatment in patients with acute ischemic stroke caused by a proximal intracranial occlusion of the anterior circulation is cost-effective over 2 years from a societal perspective. Its proven clinical effectiveness and the cost savings in rehabilitation that fully compensate for the higher intervention costs in the hospital should simplify decision making on reimbursement and implementation of endovascular treatment for ischemic stroke worldwide.

ARTICLE INFORMATION

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Drs van den Berg, Dijkgraaf, Roos, and Dippel had the original idea for this study. All authors contributed either to the acquisition of the original trial data or the creation of the dataset. Drs van den Berg and Dijkgraaf were responsible of the statistical analysis. Dr van den Berg wrote the first draft of the report. All authors contributed to the interpretation of the results, revision of the report, and have approved the final version of the article.

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Supplemental Materials

Expanded Methods
Online Tables I–IV
CHEERS checklist

APPENDIX

List of Additional MR CLEAN Collaborators and Their Affiliations

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