

Cost-Effectiveness of Thrombectomy in Patients With Acute Ischemic Stroke

The THRACE Randomized Controlled Trial

Hamza Achit, PhD; Marc Soudant, MS; Kossar Hosseini, PhD; Aurélie Bannay, PhD;
Jonathan Epstein, PhD; Serge Bracard, PhD; Francis Guillemin, PhD;
on behalf of the THRACE Investigators

Background and Purpose—The benefit of mechanical thrombectomy added to intravenous thrombolysis (IVT) in patients with acute ischemic stroke has been largely demonstrated. However, evidence of the economic incentive of this strategy is still limited, especially in the context of a randomized controlled trial. We aimed to analyze whether mechanical thrombectomy combined with IVT (IVMT) is cost-effective when compared with IVT alone.

Methods—Individual-level cost and outcome data were collected in the THRACE randomized controlled trial (Thrombectomie des Artères Cérébrales) including patients with acute ischemic stroke. Patients were assigned to receive IVT or IVMT. The primary outcomes were modified Rankin Scale score of functional independence at 90 days (score 0–2) and the EuroQol-5D quality-of-life score at 1 year.

Results—Treating acute ischemic stroke with IVMT (n=200) versus IVT (n=202) increased the rate of functional independence by 10.9% (53.0% versus 42.1%; $P=0.028$), at an increased cost of \$2116 (€1909), with no significant difference in mortality (12% versus 13%; $P=0.70$) or symptomatic intracranial hemorrhage (2% versus 2%; $P=0.71$). The cost per one averted case of disability was estimated at \$19379 (€17480). The incremental cost per one quality-adjusted life year gained was \$14881 (€13423). On sensitivity analysis, the probability of cost-effectiveness with IVMT was 84.1% in terms of cases of averted disability and 92.2% in terms of quality-adjusted life years.

Conclusions—Based on randomized trial data, this study demonstrates that IVMT used to treat acute ischemic stroke is cost-effective when compared with IVT alone.

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Key Words: quality of life ■ quality-adjusted life years ■ stroke ■ thrombectomy

Stroke is a major global health concern. The last estimation of the Global Burden of Disease Study (2013) showed that ≈6.5 million people worldwide died after a stroke and 25.7 million survived.¹ However, the most devastating impact concerns the long-term effects of such accidents in terms of physical and psychological dependence. Hence, in France, stroke represents the leading cause of nontraumatic acquired disability and the second cause of dementia.

About 130000 hospitalizations because of ischemic stroke are recorded every year in France. Because of the burden of this morbidity in terms of long-term effects, dealing with the consequences constitutes a major challenge for both the healthcare system and the National Health Insurance System (NHIS) in France. In this regard, improving treatment efficacy with new techniques is of great importance to reduce the associated morbidity.

Intravenous administration of tPA (tissue-type plasminogen activator) is the established standard treatment for stroke. Several studies have demonstrated a positive effect, especially when administered within 4.5 hours after stroke.^{2,3} However, with large proximal vessel occlusions, this treatment is associated with poor clinical outcomes.⁴⁻⁶ Combining standard treatment with endovascular treatment offers a significantly better outcome in this context.⁷⁻¹⁴ This approach combines the advantages of the 2 treatments in that intravenous thrombolysis (IVT) can be started within a short time, whereas endovascular treatment, which requires time to mobilize the interventional team, increases the rate of recanalization.

As well as having clinical benefit, the economic advantage of the combined strategy was demonstrated in various studies.

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From the Department of Clinical Epidemiology, INSERM CIC-EC 1433 (H.A., M.S., K.H., J.E.), Department of Medical Information (A.B.), and Department of Diagnostic and Interventional Neuroradiology, INSERM U 947 (S.B.), University Hospital of Nancy, France; and Department of Clinical Epidemiology, INSERM CIC-EC 1433, EA 4360 APEMAC, University of Lorraine and University Hospital of Nancy, France (F.G.).

Correspondence to Hamza Achit, PhD, CIC-1433 Epidémiologie clinique, CHRU de Nancy, 9 Allée du Morvan, 54505 Vandœuvre-lès-Nancy, France. E-mail h.achit@chru-nancy.fr

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However, most of these studies estimated cost-effectiveness based on theoretical models^{15–19} rather than empirical data.²⁰

The purpose of this study was to analyze whether mechanical thrombectomy combined with IVT (IVMT) is cost-effective when compared with IVT alone. We used data from a randomized clinical trial (THRACE [Thrombectomie des Artères Cérébrales]) to estimate the long-term effects of the 2 treatment approaches and associated costs.⁷ Analysis of cost-effectiveness was from the perspective of the NHIS in France.

Methods

Study Design

The THRACE trial compared the evolution of clinical outcome mainly in terms of functional independence at 3 months for patients with moderate to severe stroke (US National Institutes of Health Stroke Scale score of 10–25); with an occlusion of the intracranial internal carotid artery, the M1 segment of the middle cerebral artery, or the superior third of the basilar artery confirmed by computed tomography or magnetic resonance angiography; age 18 to 80 years; and receiving IVT alone or IVMT. A computer schedule was used for randomization to minimize imbalance in the number of patients between the 2 compared groups. The design and clinical results have been extensively reported elsewhere.⁷

The specificity of the THRACE trial is that benefits of the new strategy were assessed in situations of strict comparability with the standard treatment. Indeed, patients were included only if they were eligible for the new strategy as well as standard treatment. The decision to include patients with National Institutes of Health Stroke Scale score of 10 to 25 allowed for complying with comparability requirements. Indeed, in France, IVT is not recommended with the most severe ischemic stroke (National Institutes of Health Stroke Scale score of >25). By contrast, performing thrombectomy may be unjustified with minor to moderate stroke (National Institutes of Health Stroke Scale score of <10). Because both therapies are more effective when administered early, patients were included and received thrombolysis within a maximum delay of 4 hours after symptom onset.²¹ Thrombectomy had to be performed within 5 hours of symptom onset.

The study protocol was approved by the Comité de Protection des Personnes III Nord Est Ethics Committee and the research boards of the participating centers. All patients or their legal representatives provided written informed consent.

Costs

This study considered the perspective of the NHIS in France. For this purpose, we used all available information on patients and the hospital stay (age, comorbidity, hospitalization length, complications, etc) to classify each patient's stay in the appropriate Diagnosis-Related Group (DRG) by using the French NHIS rating software. DRG is a fixed tariff paid by the NHIS to hospitals for the initial procedural and hospitalization stay. It allows for funding all hospital stays in the areas of medicine, surgery, and obstetrics in all hospitals in France. Because the THRACE trial was conducted in public-sector hospitals, we considered the current rate applicable for the public sector in the year of the study (2015).

In the current DRG costing classification, treatment with IVT alone corresponds to a hospital stay for stroke classified as the nontransient cerebrovascular accident DRG, with 4 proposed tariffs that depend on the severity determined essentially by age, length of hospitalization, and occurrence of adverse events. However, with thrombectomy added to treatment, the procedure is reclassified as other acts through vascular access of nervous system DRG, with higher tariffs that also depend on severity. This DRG is used by default because of no specific DRG for the thrombectomy procedure. Certain serious events could even lead to classifying the stay with other DRGs (craniotomy, hemorrhagic transformation stroke, etc).

By evaluating the DRG rate, we considered the difference in costs during the hospitalization. This strategy, consisting of analyzing the initial extra costs with the implementation of the new procedure,

was motivated by the context of the study in which no DRG rate was established for the thrombectomy procedure. Costs were not discounted to current values because of the short-term time horizon. Discounting is needed when spending is scheduled in the future and has to be reduced to the present value.

Outcomes

The primary end point was the rate of functional independence at 3 months in the 2 treatment groups. This rate refers to a score of 0 to 2 on the modified Rankin Scale (ranging from 0, no symptoms to 6, death).²² We analyzed disability cases averted with the new strategy. The secondary efficacy outcome was health-related quality of life measured by EuroQol-5D questionnaire at 1 year from the date of stroke.

Cost-Effectiveness Analysis

The economic acceptability of a new approach to a community is analyzed by measuring first the incremental cost (ie, the additional cost per one additional unit of efficacy), that is, 1 additional quality-adjusted life year (QALY) gained and averted case of disability. Cost-effectiveness analysis with QALY scores as an outcome concerns patients who survived at least 1 year (IVT=119; IVMT=124). Second, this incremental cost was compared with the maximum cost that the decision maker is ready to pay for a 1 unit gain in health outcome (maximum willingness to pay [WTP]). Because of no fixed reference value for the maximum WTP in France,²³ we considered the maximum WTP as the value of the gross domestic product per capita for the year of the study (ie, €32 789 in 2015).

The second measure of acceptability is the net monetary benefit (NMB), which represents the difference between the community-based valuation of clinical gain and the cost for achieving this gain.²⁴

$$\text{NMB} = (\Delta E \times \lambda) - \Delta C,$$

where ΔE is the difference in effectiveness, λ is society's maximum WTP for an additional health benefit, and ΔC is the incremental cost. A positive-sign NMB indicates that the community gives greater value to clinical gain over the implementation cost, so the new treatment is thus cost-effective, whereas a negative-sign NMB indicates that costs outweighed the benefit.

Sensitivity Analysis

The robustness and sensitivity of results to the uncertainty of input variables in cost and effectiveness were explored by deterministic sensitivity analysis and probabilistic sensitivity analysis. Deterministic sensitivity analysis is used to investigate the sensitivity of results to potential variation in cost and effectiveness. We used this method to identify cost and clinical outcome variation representing the limits of cost-effectiveness. Probabilistic sensitivity analysis investigates uncertainty because of the sampling process.²⁵ Results are presented as a cost-effectiveness acceptability curve, which represents the probability that NMB is positive for a range of (λ) values of maximum WTP.

λ values enabling 5% and 95% probability of cost-effectiveness represent the confidence interval (CI) for the estimated value of NMB.

Results

Between June 2010 and February 22, 2015, 412 patients were randomized to receive IVT (n=208) or IVMT (n=204). Ten patients were excluded because of missing data or were lost to follow-up. The analyses therefore involved 402 patients.

Sociodemographic characteristics (age, sex) did not differ between the groups (Table 1). Characteristics of comorbidities were similar except for proportions of patients with diabetes mellitus, high blood pressure, and high cholesterol, which were higher with IVT than IVMT. Stroke severity did not differ between the groups, nor did stroke time management differ in terms of delay from symptom onset to IVT initiation or to randomization.

Table 1. Baseline Characteristics of Stroke Patients With Intravenous Thrombolysis Alone or Intravenous Thrombolysis Plus Intra-Arterial Thrombectomy

	IVT Alone (n=202)	IVMT (n=200)
Sociodemographic characteristics		
Age, y	62.8±14.4	62.8±13.0
≤70	119 (58.9)	120 (60.0)
>70	83 (41.1)	80 (40.0)
Sex		
Male	102 (50.5)	115 (57.5)
Female	100 (49.5)	85 (42.5)
Comorbidities, n (%)		
Hypertension	114 (57.0)	95 (48.5)
Diabetes mellitus	33 (16.6)	17 (8.7)
History of stroke	14 (7.0)	13 (6.8)
Hypercholesterolemia	105 (57.4)	79 (45.1)
Current or past tobacco use	77 (42.6)	83 (47.4)
Coronary disease	29 (15.1)	32 (16.8)
NIHSS score, median (IQR)	17 (13–21)	18 (15–21)
Workflow time, min, median (IQR)		
From stroke onset to imaging	109 (88–140)	112 (86–135)
From stroke onset to intravenous thrombolysis	153 (124–180)	150 (120–178)
From stroke onset to randomization	170 (138–198)	168 (143–195)
Safety variables		
Death at 90 d	27 (13%)	24 (12%)
Symptomatic hemorrhages at 24 h	3 (2%)	4 (2%)

IQR indicates interquartile range; IVMT, intravenous thrombolysis plus intra-arterial thrombectomy; IVT, intravenous thrombolysis; and NIHSS, National Institutes of Health Stroke Scale.

Cost-Effectiveness

Implementing the combined treatment approach resulted in average extra cost of \$2116 (€1909; 90% CI, \$1884–2348 [€1700–2118]) for the NHIS (Table 2). However, this approach led to a 10.9% increase in functional independence at 3 months after cerebral stroke (ie, with the new approach, the number of disability cases averted was increased by 10.9%). The incremental cost-effectiveness ratio, corresponding to the cost of 1 additional averted disability case, was estimated at \$19379 (€17480; 90% CI, \$10576–79822 [€9540–72000]). This incremental cost was below the WTP threshold, \$36351 (€32789) in 2015. The NMB was \$1853 (€1672; 90% CI, \$–1205 to 4911 [€–1087 to 4430]), so the benefit of IVMT outweighed the cost of implementation.

The mean QALY score was higher with IVMT than IVT by 0.12 years (Table 2). The incremental cost per one QALY gained was estimated at \$14880 (€13422; 90% CI, \$8595–47007 [€7753–42401]). Therefore, the IVMT approach was cost-effective when compared with IVT. The average incremental NMB was estimated at \$2757 (€2487; 90% CI, \$–454 to 5968 [€–410 to 5384]).

Sensitivity Analyses

Results of deterministic sensitivity analysis showed that increasing the cost of IVMT by 31.25% (ie, from \$5904 [€5326] to \$7750 [€6991]) would annihilate the expected net benefit. Therefore, this variation represents a borderline cost increase. When incremental effectiveness decreased from 10.9% to 5.8% of averted cases of disability or 0.0525 QALY (instead of 0.12 QALY), IVMT became borderline cost-effective.

Probabilistic sensitivity analysis was used to estimate the probability that the intervention was cost-effective at different threshold values of WTP. With the parametric assumptions, the cost-effectiveness acceptability curve indicated a 50% chance of cost-effectiveness when the WTP value reached the sample's incremental cost-effectiveness ratio estimate. At a threshold value of gross domestic product per capita, the probability of IVMT being cost-effective was 84.1% when considering functional independence (averting disability) and 92.2% when considering QALYs (Figure).

Discussion

We found that a combined strategy of intravenous tPA followed by IVMT for acute stroke within 4 hours of symptom onset was cost-effective when compared with intravenous tPA alone (IVT) when considering averted cases of disability and QALYs. This result was obtained even though the THRACE trial had the lowest estimation of additional benefit found in the literature. Indeed, using the same outcome of functional independence, namely, a modified Rankin Scale score 0 to 2 at 90 days, similar trials found a higher estimation of incremental performance: Berkhemer et al,¹¹ 13.5% (32.6% versus 19.1%); Jovin et al,¹⁰ 15.5% (43.7% versus 28.2%); Goyal et al,⁸ 23.8% (53.0% versus 29.3%); Saver et al,⁹ 25% (60% versus 35%); Campbell et al,¹² 31% (71% versus 40%).

The difference in effectiveness between the THRACE trial and the previous studies could be mainly explained by first, beyond a demonstration of proximal artery occlusion, imaging criteria not used to select patients, and second, the delay from IVT to randomization being shorter in the THRACE trial (<20 minutes) than in the other trials. Hence, patients were enrolled before knowing the effect of thrombolysis. The other studies reported a longer delay of randomization, which therefore excluded fast responders to thrombolysis.^{8,10,11}

One similar study reported an estimation of additional cost of the combined strategy based on the DRG. However, the estimation was in the US context.¹⁶ The additional cost was estimated at \$10840. In other studies,²⁰ costs were estimated by a microcosting approach so additional costs could not be compared.

The cost-effectiveness of IVMT was analyzed by considering a high-level requirement concerning the maximum WTP amount. In this respect, the World Health Organization recommends an incremental cost below 1 to 3 times the gross domestic product per capita and considers a new approach as very cost-effective with an incremental cost <1 gross domestic product per capita.^{26,27}

From the French register of stroke cases, we estimated the number of patients eligible for the new treatment approach IVMT.²⁸ Register-based statistics showed that between 2006

Table 2. Cost-Effectiveness of the Intravenous Thrombolysis Plus Intra-Arterial Thrombectomy Approach, With Averted Disability and Utilities as Outcomes

	IVT	IVMT	Incremental Difference
	(n=202)	(n=200)	
Outcome: disability at 90 d			
NHIS costs	\$3788 (€3417)	\$5904 (€5326)	\$2116 (€1909)
Modified Rankin Scale score 0–2 at 90 d, %	42.1	53.0	10.9
Cost-effectiveness statistics			
Incremental cost-effectiveness ratio: \$19 379 (€17 480) (90% CI \$10 576–79 822 [€9540–72 000])			
Net monetary benefit at threshold of \$36 351 (€32 789): \$1853 (€ 1672) (90% CI \$–1205 to 4911 [€–1087 to 4430])			
	(n=119)	(n=124)	Incremental difference
Outcome: utility at 1 y			
NHIS costs	\$3426 (€3090)	\$5336 (€4813)	\$1910 (€1723)
Utility	0.46	0.58	0.12
Cost-utility statistics			
Incremental cost-utility ratio: \$14 880 (€13 422) (90% CI \$8595–47 007 [€7753–42 401])			
Net monetary benefit at threshold of \$36 351 (€32 789): \$2757 (€2487) (90% CI \$–454 to 5968 [€–410 to 5384])			

CI indicates confidence interval; IQR, interquartile range; IVMT, intravenous thrombolysis plus intra-arterial thrombectomy; IVT, intravenous thrombolysis; and NHIS, National Health Insurance System.

and 2010, the incidence of stroke that met our inclusion criteria was 14.7/100 000 person-years, corresponding to 6765 people in the total French population per year. Thus, the total additional cost of implementing IVMT instead of IVT was estimated at ≈\$14.3 (€12.9) million per year. However, this cost would avoid death or disability for ≈737 patients each year.

Strengths

This economic evaluation of a combined strategy, IVMT, for treating acute ischemic stroke is among the first based on empirical data at an individual level for both cost and effectiveness data. This specificity also allowed for data-driven examination of uncertainty and conducting sensitivity analysis. The other originality of this study relates to THRACE trial, with its estimation

of performance conducted under representative conditions of clinical practice. The objective was to highlight the gain in efficiency only when thrombectomy is justified and effective, that is, neither for minor stroke nor with late management, which could cause irreversible harm. Thus, the results of the present study are directly applicable to the French population.

Limitations

The main limitation of this study is that we considered only costs of implementation and hospital stay for the NHIS in France. Costs of outpatient care, including medical visits and rehabilitation, were not considered. However, in terms of the better clinical outcomes with IVMT than IVT at 1 year, we think that differences in healthcare costs between

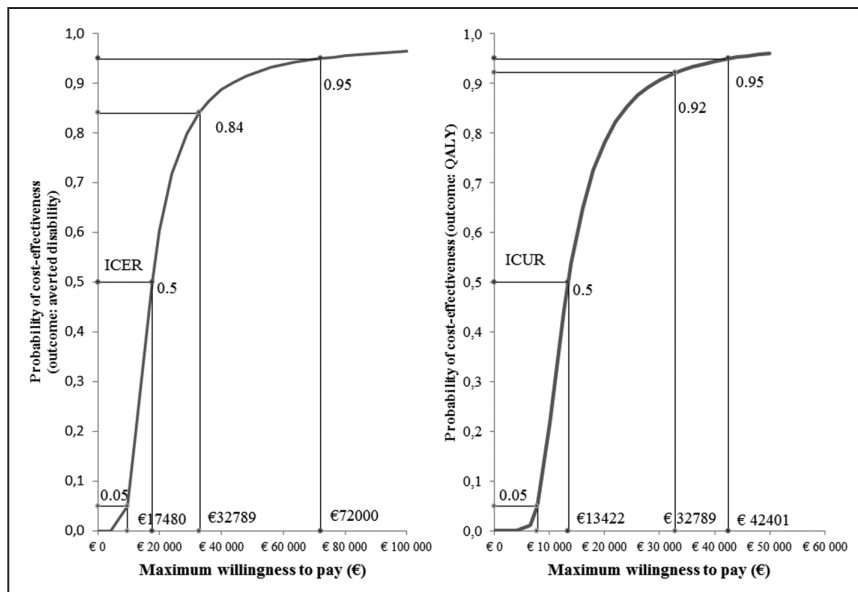


Figure. Cost-effectiveness acceptability curve analysis. ICER indicates incremental cost-effectiveness ratio; ICUR, incremental cost-utility ratio; and QALY, quality-adjusted life year.

the strategies would be lower when considering all costs. More precisely, the extra cost caused by thrombectomy as an additional intervention may be offset by less healthcare use in the ambulatory environment. This situation would lead to a lower incremental cost per unit efficacy. Therefore, decisions would favor implementing the new treatment strategy. Another limitation concerns attrition bias in cost-utility analysis. Indeed, because patient quality of life was measured at 1 year after the accident, a large proportion of patients were lost to follow-up because of death or nonresponse. However, the attrition ratio was similar for the 2 groups: IVT, 41.1%; IVMT, 38%.

Conclusions

Based on randomized trial data, this study demonstrates that IVMT used to treat acute ischemic stroke is cost-effective when compared with IVT alone.

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Disclosures

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