COST-EFFECTIVENESS OF THROMBOLYSIS WITH ALTEPLASE IN PATIENTS WITH ACUTE ISCHEMIC STROKE IN SLOVAKIA

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INTRODUCTION

Ischemic stroke (IS) is the second most common single cause of death in Europe. It is responsible for more than one million deaths per year and is the leading cause of long-term disability (1; 2). The Eurostat report (2013) pointed out 11 000 avoidable deaths (to 75 years) in the Slovak Republic (SR) of which 16% were attributable to IS (3).

Intravenous thrombolysis (IVT) with alteplase (Actilyse®, Boehringer Ingelheim), a recombinant tissue plasminogen activator, has proven treatment benefit for the emergency management of IS (4). IVT is recommended in IS patients with stroke onset up to 4.5 h (5). Treatment of acute IS must be started as early as possible within 4.5 hours after onset of stroke symptoms. The treatment effect is time-dependent; therefore, earlier treatment increases the probability of a favourable outcome (6).

OBJECTIVE

The aim of this study was to estimate cost-effectiveness of systemic intravenous thrombolysis (SIT) with alteplase in comparison with strategy without SIT in the population of IS patients in Slovak setting from the perspective of the Slovak healthcare system.

METHODS

The analysis followed the legislation and methodological guidelines of SR.

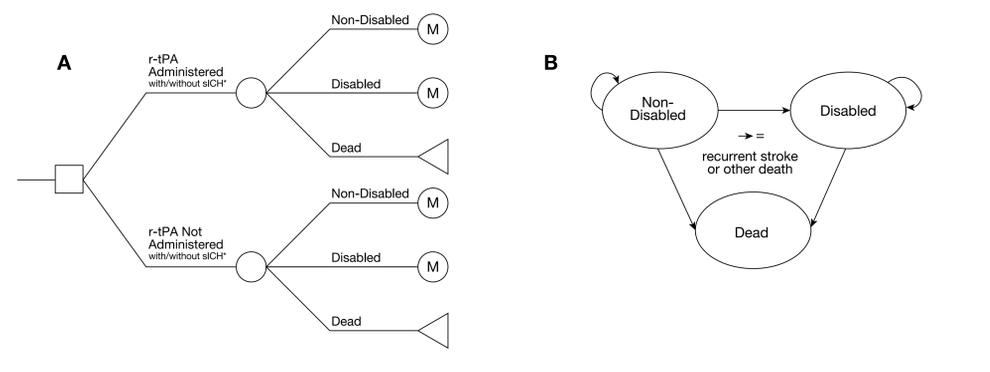### Model description, time horizon and patients´ characteristics

The cost-utility analysis was carried out from the payer perspective.

An economic model (decision tree + Markov model) simulating patients with acute ischaemic stroke who do or do not receive alteplase within 4.5 hours from onset of symptoms was used and adapted to local conditions. Patients were modelled through 3 possible health states: independent (modified Rankin scale score of 0–2), dependent (modified Rankin scale score of 3–5) and dead (7).

The model consists of 3 time phases: 0 to 6 months when the treatment effect of alteplase was assumed to be observed at 6 months; from 6 to 12 months when no further treatment effect was assumed and patients could move from the independent or dependent state to any other health state with equal probabilities for both treatment arms; and beyond 12 months when also no further treatment effect from alteplase was assumed and patients in the dependent state at 12 months and beyond do not move to an independent state, and that people in the independent state at 12 months and beyond do not move to a dependent state unless they survive a recurrent stroke.

The model assumed a lifetime horizon with a cycle length of 6 months for the first 12 months, followed by cycles of 12 months thereafter.

FIGURE 1   Scheme of the economic model (7)

Treatment
Management with thrombolytic treatment (Actilyse) vs. without thrombolytic treatment (comparator)

Population
Population of interest were patients with acute IS within 4.5 hours from symptoms onset. The characteristics of patients related to gender (female proportion 43.7%) and age (70 years) was taken from National Health Information Center (8).

Clinical inputs
For the standard treatment arm (reference arm), the proportion of patients in each health state at month 6 was informed by the Lothian stroke registry (9; 10).

For alteplase arm the proportion of patients in each health state at month 6 was estimated by applying relative risks of death (RR: 0.89, CI 95 %: 0.67- 1.18; p=0.41) and dependence or death (RR: 0.83, CI 95 %: 0.75- 0.92; p<0.001) taken from meta-analysis (9; 10).

In the first phase symptomatic haemorrhage associated with extra costs could occur in 0.25% patients with standard treatment and 1.04% patients with alteplase (9).

In the phase 2 patients moved between states with the same transitions probabilities in both arms taken from the Lothian stroke registry (Table 1) (9; 10).

For the third phase of the model (beyond 12 months), the annual risk of a recurrent stroke (0.05), and the associated risk of mortality (0.25), were taken from the Lothian stroke registry (9; 10).

TABLE 1   Transition probabilities

Distribution of patients at 6 and 12 months by functional outcome	Phase	State	Outcome at the end of phase		
			Independent	Dependent	Dead
Standard Treatment	*6 months*		39.53%	32.56%	27.91%
	12 months	Independent	87.50%	11.11%	
		Dependent	9.38%	74.07%	
		Dead	3.12%	14.80%	
Alteplase	*6 months*		49.81%	25.35%	24.84%
	12 months	Independent	87.50%	11.11%	
		Dependent	9.38%	74.07%	
		Dead	3.12%	14.82%	

To estimate the mortality risk for patients who did not have another stroke, general mortality taken from The Statistical Office of the Slovak Republic, 2017 (11) was adjusted by a factor of 2.3 (the Perth Community Stroke Study) to reflect the higher mortality rates among people who have had a stroke compared with the general population.

Cost data
Cost of alteplase (0.9 mg/kg, assuming 76 kg patient weight) came from official list of medicines prices and costs for health states were taken from local sources (€ 844.50) (12; 13).

Costs of administration of treatment related to alteplase were assumed to be covered by the cost of hospitalization.

Health states direct costs were taken from qualitative cross-sectional survey (13) (Table 2).

TABLE 2   Health states direct costs

Health status	Time period	Overall cost
Cost of independent stroke year 1	1th year	€ 2,839.72
Cost of independent stroke post-year 1	2nd year +	€ 1,518.74
Cost of dependent stroke year 1	1th year	€ 6,255.70
Cost of dependent stroke post-year 1	2nd year +	€ 2,709.49
Cost of acute even fatal stroke	30 days	€ 2,687.97
Cost of haemorrhage (CT scan)	event	€ 158.32

Utility data
Utility values (0.74 for the independent state and 0.38 for the dependent state) and data on quality of life came from trial that collected EQ-5D utility values in a sample of 147 patients from the Lothian stroke registry (9; 10).

Discounting
A yearly discount rate of 5% for costs and health outcomes was applied in line with methodological guidelines in SR.

Outcomes
The lifetime (40 years) outcomes estimated in the analysis were: life years (LY), quality-adjusted life years (QALY), costs and incremental cost-utility ratio (ICUR).

Sensitivity analysis
One-way sensitivity analysis with variables varied by +/- 30 % in line with Slovak guidelines tested the impact of the main model variables individually on ICUR.

RESULTS

Long-term effectiveness
Higher percentage of surviving population in independent status was recorded in treatment arm with thrombolysis (Figure 2).

Administration of alteplase was associated with an improvement in survival (undiscounted increment of 0.305 LYs) and QALYs (discounted increment of 0.267 QALYs) compared to treatment without thrombolysis (Table 3).

Long-term costs
With higher costs and QALY gain, ICUR of € 2,696 per QALY is below lowest possible threshold value determined by the Slovak law € 26,712/QALY. Thrombolytic treatment with alteplase thus can be considered to be highly cost-effective in Slovak setting (Table 3).

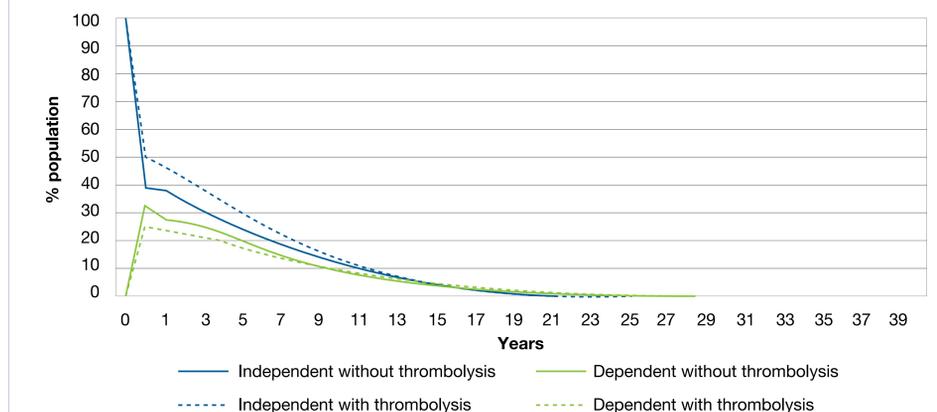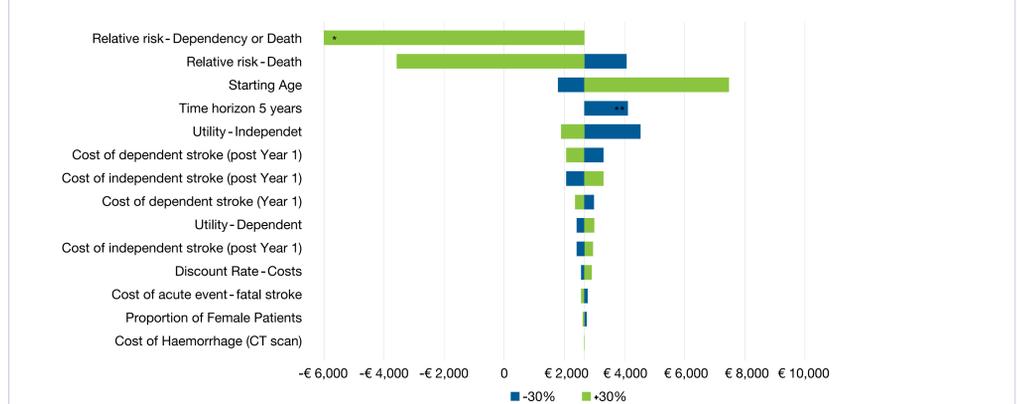### FIGURE 2   Surviving of patients in health states by treatment arms, lifetime horizon (not discounted)

TABLE 3   Cost-effectiveness results

Result	Treatment with thrombolysis	Treatment without thrombolysis	Difference
Total cost (5 % DR)	€ 11,586	€ 10,867	€ 719
QALY (5% DR)	2.651	2.384	0.267
LY (no DR)	5.715	5.411	0.305
ICER (€/LY)			€ 3,113
ICUR (€/QALY)			€ 2,696

DR= discount rate, ICUR= incremental cost-utility ratio, LY= life years, QALY= quality adjusted life years

FIGURE 3   One-way sensitivity analysis

*Thrombolysis with alteplase is dominant when the parameter is decreased by 30% and dominated when the parameter is increased by 30%.
**Scenario analysis with time horizon 5 years (vs. base case lifetime horizon 40 years).

CONCLUSIONS

Based on the analysis, thrombolysed patients with alteplase after IS survived longer and their survival without disability was also higher. Their QALY gain was higher compared to patients without thrombolysis. Treatment with alteplase required higher cost but it still can be considered to be highly cost-effective strategy in the Slovak setting.

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