Burden of stroke in Italy: an economic model highlights savings arising from reduced disability following thrombolysis

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Abstract

Background

The consequences of stroke must be assessed not only in terms of incidence and mortality rates, but also in terms of disability, which may persist long after the acute phase.

Thrombolysis, if timely administered, can effectively reduce post-stroke disability.

Aims

The economic model presented herein aims to evaluate, in eligible patients, the effects of alteplase on post stroke disability and related costs over three years.

Methods

The economic analysis was developed on the basis of four key components: clinical outcomes from international trials, economic consequences extracted from cost of illness studies, regulatory data from national and international agencies, and national epidemiological data.

A population-level model estimated the difference in disability costs between patients treated with standard care versus those receiving thrombolytic therapy within 4.5 hours of acute ischemic stroke. The analysis covered 36 months from discharge.

Results

Reduced costs related to post-stroke disability were observed in treated patients compared to those receiving standard care (control).

The overall savings were € 2,330.15 per average patient: € 1,445.81 during the first 18 months, € 362.25 between 18-24 months, and € 522.09 in the 24-36 months period.

The overall savings on 3,174 Italian treated patients in 2013 were € 7,395,907 over three years.

Conclusion

Our study reveals that performing thrombolytic therapy in eligible patients improves economic outcomes compared to patients receiving standard care.

This model is useful for decision makers, both within and outside of the Italian national context, as a tool to assess the cost-effectiveness of thrombolysis in both short and long term period.

Introduction

Stroke is the second leading cause of death worldwide; in 2010 there were 16.9 million new stroke cases, 5.9 million deaths related to the disease, and 102 million Disability Adjusted Life Years (DALYs) lost.(1) Nevertheless the burden of stroke may be underestimated because of the consequences of stroke after the acute phase.(2). Even if the patients with acute strokes are managed optimally, they face the risk of severe disability (30%) and require institutional care (20%) after stroke.(3) Thus, the true impact of stroke must be viewed not only in terms of incidence and mortality rates, but also in terms of disability, which often persists for an extended time, often permanently, after stroke.(4)

In Italy, the epidemiology of stroke is similar to that of other high-income countries, with ischemic stroke accounting for about 80% of total cases.(5)

Thrombolysis using recombinant tissue Plasminogen Activator (rtPA), in Italy, is currently the only available evidence-based pharmacotherapy to treat acute ischemic stroke.(6) he European Medicine Agency approved alteplase for the fibrinolytic treatment of ischemic stroke for the European union(7); in Italy, the marketing authorization with the extended indication was approved in 2003.

The Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST), which was completed in 2006, showed the safety of thrombolysis administered within 3 hours after ischemic stroke.(6) To ensure the maintenance of high levels of efficacy and safety in Italy, patients treated with alteplase must be registered in the “Safe Implementation of Thrombolysis in Stroke-Italian Stroke Thrombolysis Register” (SITS-ISTR)(7), which represents an extension of the previous SITS-MOST study.

Evaluations based on SITS-ISTR also demonstrated the safety and efficacy of thrombolytic treatment between 3 and 4.5 hours of onset of ischemic stroke.(8) Most recently, in 2013, hospital centers in Italy were authorized to administer alteplase up to 4.5 hours after acute ischemic stroke.

Several trials, both ongoing(8) and completed(9), have demonstrated a positive risk/benefit ratio between 4.5 and 6 hours after the ischemic event.

In each minute following a typical large vessel acute ischemic stroke, 1.9 million neurons, 14 billion synapses, and 12 km (7.5 miles) of myelinated fibers are destroyed.(10) The effectiveness of reperfusion measured by clot dissolution varies according to the time interval between ischemic stroke and alteplase administrationaccording to Meretoja *et al.*, each minute of onset-to-treatment time saved could grant, on average, 1.8 days of extra healthy life.(11)

The main parameter in evaluating the efficacy of thrombolytic treatment is the assessment of post-stroke disability compared with standard care. Various qualitative scales are currently in use to measure disability following an ischemic stroke.(12)

Data related to the effectiveness of thrombolytic therapy, included in our economic model, were extracted from international trials which use the Oxford Handicap Scale (OHS) as a measure of disability. Data costs related to the different levels of post stroke disability were extracted from economic studies which use the modified Rankin Scale (mRS). Both scales consist of 5 levels of disability, from no disability to complete dependence, and are substantially overlapping.(9)

The burden of stroke has an impact on healthcare costs in addition to patient's quality of life. In contrast to most of the diseases characterized by full recovery, however, the neuronal damage results in a disability that is minimally recoverable one year after the ischemic event. This means that it is necessary to evaluate the costs of stroke not only in the short term (30-90 days), but also in the medium and long term (1-3+ years). Thrombolysis is the only acute treatment that can effectively reduce post stroke disability. In many high income countries, like Italy, thrombolysis allows many patients to be effectively treated (13, 14) with consequent savings in both economic and clinical terms (quality of life).

Aims

The goal of the economic model was to demonstrate the reduction in post-stroke disability following thrombolysis and to quantify the associated costs over three years after the ischemic event using an increase in the rate of patients treated with alteplase on the total number of eligible patients.

Materials and methods

We developed a population-level model to estimate the difference of disability-costs between patients treated with standard care and those treated with thrombolytic therapy within 4.5 hours of acute ischemic stroke.

All data were extracted from a scientific literature search.

The economic evaluation was based on a societal perspective, which is the most appropriate in a public health system such as the Italian one.

Study design – economic data

The baseline cost data were estimated according to the following components:

1. Direct healthcare costs, including: additional stroke-related hospital admissions, clinical consultations, diagnostic tests and procedures, domiciliary care, medical therapies, rehabilitation services, and other healthcare costs (i.e. appliances, aids)
2. Direct non-healthcare costs, including informal care and paid care
3. Indirect costs, including productivity losses

These costs were obtained from a cost of illness analysis published in 2012 by Fattore *et al.*(15), which was based on a sample of 546 Italian patients with stroke; the study described in detail how the mRS level of post stroke disability influenced direct medical costs, direct non-medical costs, and indirect costs.

Each class of costs (figure 1) was further divided into 3 disability levels:

1. No or mild disability, mRS 0-2

2. Moderate disability, mRS 3
3. Severe disability, mRS 4-5

Hence, each level was evaluated up to 18, 24, and 36 months.

These time-points were chosen based on international health economic studies of intravenous thrombolysis treatment for acute ischemic stroke, indicating that intervention may be cost-effective in both the short term and in the long term(16, 17). However, the modeling of long-term costs and effects are subject to both uncertainty and methodological problems.(18)

The percentage changes in costs for each class of disability after 12, 24, and 36 months were calculated from data published by Lopez *et al*.(19)

Considering that clinical data included in our model showed the distribution of disability post-acute stroke at 18 months, we calculated the costs at 18 months, inferring that the variation between 12 and 24 months was linear.

Study design – clinical data

The effectiveness of thrombolysis was assessed in terms of difference of post-stroke disability between patients treated with alteplase or standard care; data were extracted from the IST-3 trial.(9)

This international, multicenter trial measured mortality and disability at 18 months between patients treated with or without alteplase for up to 6 hours after the ischemic event.

According to data published in the IST-3 trial, thrombolysis does not significantly affect the mortality of post-stroke patients up to 18 months. Although mortality data do not substantially affect our economic analysis, we have had to consider this parameter from 18 to 36 months using data from other published trials .

The percentage changes of post stroke mortality, after 18 months,(table 1) were were extracted from the study by Slot *et al*.(20); the data on mortality published in this study are consistent with other international studies(21, 22) also conducted in the Italian population(23, 24), but more detailed and stratified by mRS classes. study did not evaluate the trend of disability after thrombolytic treatment, it did assess the probability of mRS class change, regardless of past events.(Table 1)

In the second and third year after the ischemic event, trends of mortality were assumed to be different for each disability class and stable over time within the same mRS class, regardless of alteplase administration were equally likely to change their mRS disability level over time..

Study design – population

The therapeutic indications of alteplase have changed in Italy in recent years. For most of 2013, the thrombolytic therapy could be administered within 3 hours after the ischemic event, but starting in October 2013, the window of treatment was extended to 4.5 hours. The leading Italian hospital of the SITS-MOST study prepares regular reports based on the number of thrombolytic treatments for stroke in Italy. Additionally, they publish the number of eligible patients who could have received alteplase in approved centers annually, thereby enabling the calculation of the ratio between treated and eligible patients as a measure of efficiency of the Regions (efficiency = (n treated / n eligible) *100). Data published by the coordinating centers of the SITS-MOST study are calculated by utilizing an algorithm that extracts data from recent Italian clinical trials.(25, 26)

Our analysis has been expanded to include the number of patients treated within the new 4.5 hour window for the 2013 calendar year. This is supported by the national SITS-MOST coordinating center, which demonstrated that increasing the therapeutic window to 4.5 hours for alteplase could nearly double the number of eligible patients to treatment.

The population is calculated by the SITS-MOST coordinating center based on stroke incidence, the average time between onset of stroke and hospital arrival, and on the ”door to needle time,” which is the elapsed time between arrival at the hospital and treatment administration.

Finally, the last required data in our projections are those concerning the Italian population, which were extracted from the Italian Institute of STATistics (ISTAT) report.(27)

Sensitivity analyses

Sensitivity analyses were performed to test the robustness of the results of the model, given the uncertainty in the input values for the parameters.

One-way sensitivity analyses were performed by changing rate of treated patients on eligible patients. By altering the input values across the range of possible values of 50, 75, and 100%, we identified

how the model results would change. We considered the following possible values shown in the SITS-MOST report that highlights the efficiency in every Italian region.

1.87% in worst region in Italy

33.23% in the best Italian region

50% 75% and 100% like possible future better standard values.

In addition, a 2-way sensitivity analyses was performed by simultaneously altering the input values for 2 parameters together to assess their combined effects on the results of the model.

The first parameter was the direct non-healthcare costs at 12 months and indirect costs at 12 months.

Direct healthcare, non-healthcare and indirect costs can affect various proportions on total costs as revealed in several cost of illness studies on stroke diseases.

In the sensitivity analysis these costs were calculated as direct health care from Fattore et al., multiplied by values obtained by the study of Lopez: 2.134 and 0.385, respectively, and by value obtained by the Olesen's study: 0.393 and 0.116, respectively.

The second parameter was the % treated of eligible patients.

Results

According to 2011 ISTAT census report and most recent SITS-MOST Italian report, the Italian population in 2013 was 59,685,227. The eligible patients for alteplase therapy was calculated to be 21,316. The number of patients treated with alteplase was 3,174, equal to 14.89% of eligible people.

The direct healthcare, direct non-healthcare, and indirect costs by disability classes are shown in Table 2.

In our analysis conducted for disability classes, the estimated average cost per person increased from No or Mild disability to Severe disability. , the average cost for the patient with or without Mild disability is € 6,220.54, with Moderate is € 16,586.96 and with Severe is 42,365.74; in 18-24 months range is € 1,719.18, € 4,584.18 and € 11,708.73, respectively and from 24 to 36 months is € 3,052.49, € 8,139.42 and € 20,789.38, respectively.

Direct non-healthcare costs make up the largest proportion: 58% of the total average per person cost in each disability class after 18 months, 72% after 24 months, and 73% after 36 months. The indirect costs make up the smallest proportion: 4%, 3% and 3% after 18, 24 and 36 months, respectively.

The estimated average cost per person is € 10,992.23 at 36 months after discharge for patient with No or Mild disability, € 29,310.55 for patients with Moderate disability and € 74,863.85 for patients with Severe disability.

Consequently, the costs related to the post ischemic stroke disability in patients treated with alteplase compared with those treated with standard care (control) at 36 months from discharge are lower.

The savings are € 7,395,907: € 4,588,996 for lower costs during the first 18 months, € 1,149,783 during the period 18-24 months and € 1,657,129 after 36 months (Figure 2).

Univariable (1-way = percent of treated on eligible patients) sensitivity analyses indicated that alteplase therapy is economically advantageous over the full range of possible percent treated of eligible patients values (Figure 2).
Varying percent treated of eligible patients from 1.87%, to 14.89%, 33.23%, 50%, 75% and to 100%, the savings, in Italy after 36 months, increase from € 928,820 to € 7,395,907, € 16,505,193, € 24,834,776, € 37,252,165, and € 49,669,553, respectively.

Multivariable (2-way = percent treated + different distribution costs rates) sensitivity analyses revealed that thrombolysis is again advantageous (Figure 3). Using costs distribution from Lopez et

al. study(19) in comparison with baseline data, we obtained a savings increase in a range € 558,526 to € 29,867,695 with the change of percent of treated on eligible patients from 1.87% to 100%.

Using European costs by Olesen's et al.(28) in comparison with baseline cost data, savings decrease in a range from € 946,842 to € 50,633,257 with the change of percent treated on eligible patients from 1.87% to 100%.

Discussion

Starting from the evidence (from IST-3 trial data) that thrombolysis reduces disability of patients after ischemic stroke, our study reveals that performing rtPA administration therapy in eligible patients improves economic outcomes compared to standard care.

1-way sensitivity analyses assessed a range of savings from € 2,125,094 to € 47,122,696 in Italy and revealed that across these different thresholds most of the saving is in the 18 months period post-discharge.

2-way sensitivity analyses demonstrated that thrombolysis is also cost-effective for various changes in the direct non-healthcare costs at 12 months and indirect costs at 12 months.

Additionally, savings were modelled conditional on alteplase administration within 6 hours of acute ischemic stroke. The eligible patients to thrombolysis are calculated as treatable after maximum of 4.5 hours from stroke onset. As published by Saver et al., the sooner the reperfusion of the ischemic brain area occurs then less the permanent brain damage can occur.(10)

Consequently, we consider that Italian differences of mRS disability classes between treated and untreated patients, at 18, 24, and 36 months after discharge, could be higher than data from IST-3 trial. This potential consistent difference could significantly increase the savings arising from thrombolytic treatment in our projections according on higher efficacy of the thrombolysis and then of the lower post stroke disability.

There are several limitations to our model. First, we modelled the difference of disability-costs between patients treated with standard care and treated with thrombolytic therapy on disability levels performed in one study (IST-3) without altering this outcomes in a sensitivity analysis, calling into question the generalizability of the model. This approach can be justified by a lack of adequate long-

term data. Currently, international studies provided evidence about post stroke disability states measured 90 days after treatment for acute ischemic stroke, but does not show longer-term data.(29)

However this approach had the advantage of being based on an international and multicenter trial involving 12 countries and of assuming that thrombolysis lead to relevant improvement in disability so as confirmed by numerous other trials.(6, 7, 9)

Second, our model used literature costs and survival data, so the savings could be higher or smaller in various countries. However, the model is sufficiently explained so as it allows the external validation.

Lastly, our savings were calculated with time periods limited to 18-36 months and were estimated on the survival rates from Slot et al.(20) There was a trend of decreasing survival with increasing modified Rankin Scale at 12 months and these survival rates decrease in each category of functional status during the following years. Thrombolysis was associated with lower disability than standard care; consequently it is likely that savings may be continue until patients survive.

Our economic model allows to calculate the potential savings from thrombolytic treatment in Italy, since we included national data about costs, epidemiology, and hospital efficiency related to the thrombolysis in our country. However, our study provides insight into the extent of the savings arising from the reduction of disability at 1, 2 and 3 years in a high-income country. As shown by our findings, the efficiency of Italian hospitals has plenty of scope for improvement, and considering the potential savings in both economic and in DALYs areas, it would be important to develop strategies that could significantly increase the ratio between treated and eligible patients.

Several recent economic evaluations in literature, developed in different countries with different health care systems(13, 14, 30), agree that the increase in the rate of thrombolysis is cost-effective.

However, differently from the economic studies above mentioned, our economic model is focused only on the savings arising from the reduction of post stroke disability after thrombolysis, because we think it is important to raise awareness of all stakeholders on this particular outcome.

Finally, we believe our model is useful for decision makers, even outside of our national context as a helpful tool to assess the implementation of thrombolysis as cost-effective health technology in both the short and, especially, over the long term period.

Disclosure none

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Oxford Handicap Scale	*Alteplase Therapy at 18 months*	*Traditional Therapy at 18 months*	*Variation of survival percentage between 18 and 24 months (%)*	*Variation of survival percentage between 24 and 36 months (%)*
0	0.11	0.07	-1.02	-6.25
1	0.12	0.13	-2.02	-2.11
2	0.12	0.11	-2.58	-8.70
3	0.12	0.12	-5.73	-10.59
4	0.07	0.1	-8.15	-16.88
5	0.09	0.1	-8.11	-17.74

Table 1. Percentage of patients in each OHS class after 18 months and variations by Slot et al. at 24 and 36 months from discharge

ale	**Direct healthcare costs**	**Direct non Healthcare costs***	**Indirect costs****	**Direct healthcare costs†**	**Direct non Healthcare costs††**	**Indirect costs†††**	**Direct healthcare costs‡**	**Direct non Healthcare costs‡‡**	**Indirect costs‡‡‡**	**Direct healthcare costs§**	**Direct non Healthcare costs§§**
	Discharge-12 months	**Discharge-18 months**					**18-24 months**			**24-36 month**	
2]	1,964.80	2,359.72	176.83	2,391.16	3,606.84	222.54	426.36	1,247.11	45.71	742.69	2,220.50
]	5,239.10	6,292.16	471.52	6,375.98	9,617.57	593.41	1,136.88	3,325.41	121.89	1,980.38	5,920.92
5]	13,381.50	16,071.18	1,204.34	16,285.29	24,564.80	1,515.66	2,903.79	8,493.62	311.32	5,058.21	15,122.98

healthcare-costs multiplied by 1.201

-healthcare-costs multiplied by 0.09

healthcare-costs at 12 months + costs at 12 multiplied by 0.217

-healthcare-costs at 12 months + costs at 12 months multiplied by 0.529

ect-costs at 12 months + costs at 12 months multiplied by 0.259

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healthcare costs at 12 months multiplied by 0.217

t-healthcare costs at 12 months multiplied by 0.529

rect-costs at 12 months multiplied by 0.259

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healthcare-costs at 12 months multiplied by 0.378

-healthcare-costs at 12 months multiplied by 0.941

ect-costs at 12 months multiplied by 0.505

Table 2. Costs per patient included in the model