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Budget Impact Analysis of Thrombolysis for Stroke in Spain: A Discrete Event Simulation Model

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ABSTRACT

Objective: Thrombolysis within the first 3 hours after the onset of symptoms of a stroke has been shown to be a cost-effective treatment because treated patients are 30% more likely than nontreated patients to have no residual disability. The objective of this study was to calculate by means of a discrete event simulation model the budget impact of thrombolysis in Spain.
Methods: The budget impact analysis was based on stroke incidence rates and the estimation of the prevalence of stroke-related disability in Spain and its translation to hospital and social costs. A discrete event simulation model was constructed to represent the flow of patients with stroke in Spain.
Results: If 10% of patients with stroke from 2000 to 2015 would receive thrombolytic treatment, the prevalence of dependent patients in 2015 would decrease from 149,953 to 145,922. For the first 6 years, the cost of intervention would surpass the savings. Nevertheless, the number of cases in which patient dependency was avoided would steadily increase, and after 2006 the cost savings would be greater, with a widening difference between the cost of intervention and the cost of nonintervention, until 2015.
Conclusion: The impact of thrombolysis on society's health and social budget indicates a net benefit after 6 years, and the improvement in health grows continuously. The validation of the model demonstrates the adequacy of the discrete event simulation approach in representing the epidemiology of stroke to calculate the budget impact.
Keywords: budget impact analysis, pharmaceuticals, simulation models, stroke.

Introduction

Stroke results in a marked mortality rate at the time of the acute event and during the following years [1]. Furthermore, a consequence of brain damage in one-third of patients is the development of a disability that persists over a period of time [2,3]. Thrombolysis, notwithstanding its limited influence in reducing mortality, is the only specific treatment for the acute event that improves the prognosis in patients who have had an ischemic type of stroke [2,4]. It has been shown to be cost-effective within the first 3 hours after the onset of symptoms of a stroke, despite its high cost as a pharmaceutical, because treated patients are 30% more likely than untreated patients to have no disability at 12 months [5–7]. In Spain approximately 60,000 patients with first-ever stroke are hospitalized each year [3]. Given this volume, decision-makers need an economic approach to fully understand the impact of the introduction of thrombolysis on a population level in terms of the budget of the Spanish health system and the resulting health gain [8,9]. Mauskopf has described budget impact analysis (BIA) as an estimate of the impact of a new treatment on annual costs, annual health, and other outcomes of interest for the first, second, and subsequent years after the introduction of the new product for a national or a health-plan population [10]. With a similar purpose, but from a different approach, the business literature uses the concept of return of investment. This term indicates the cash flow over a specified period of time. As a measure of profitability, BIA shows the net trade-off between cost and revenues of a project in relationship with the investment [11]. The BIA of stroke treatments relies on both incidence and prevalence [12–14]. In the assessment of the burden of neurologic diseases, the societal perspective must be applied because the management of the long-term consequences in terms of disability entails an important consumption of resources. The calculation of these costs is based on the change in prevalence of disabled patients [14].

In practice, BIA is usually carried out on the basis of the pharmaceutical costs by straightforward spreadsheets. These costs are usually elaborated for submission to the government drug agency in the process of registering a new treatment. The lack of a standard and well-accepted methodology has led to a scarcity of these studies in the scientific literature. In recent years, however, different scientific societies and governmental agencies have recognized the important role that BIA can play as a complementary tool for cost-effectiveness analysis in the decision-making process for new technologies [15–17]. At the same time, different authors have published guidelines to promote good practices [18–20].

In the field of economic evaluation, different approaches for disease modeling have been applied. Markov models have become the most popular technique because their management of a cohort produces an output that fits well with the needs of cost-effectiveness studies [20,21]. Modeling of stroke for BIA requires different outputs because the key parameter is the population prevalence. Discrete event simulation (DES), which is widely used in business and engineering, is an alternative to Markov models. It has been applied in health services to evaluate cases on waiting lists for surgical procedures. Nevertheless, the flexibility of DES in the representation of different stages of disease and in the calculation of various outputs has promoted its growing presence in the economic evaluation of health interventions [22,23].

The objective of this study was to calculate the BIA of thrombolysis in the treatment of stroke in Spain by means of a DES model that represents the flow of patients with stroke in the Spanish population.

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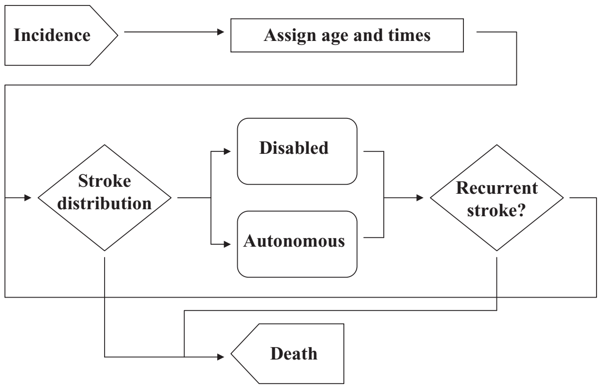

Figure 1 Simplified diagram of the model.

Methods

The BIA of stroke treatments relies on both incidence and prevalence. The incidence of stroke is required to estimate the intervention costs, and it can be obtained from the Minimum Data Set of the health system; the calculation of costs related to the care of disabled individuals is based on its prevalence. We constructed a DES model to represent the natural history of stroke in the Spanish population to calculate the prevalence of stroke-related disability from 2000 to 2015.The number of disabled subjects was obtained twice; the first considered that thrombolysis was not used (base conditions), and the second took into account that from the year 2000, 10% of all strokes were treated with the drug recombinant tissue plasminogen activator (rt-PA) within 3 hours of the onset of symptoms, according to the conditions of the National Institute of Neurological Disorders and Stroke (NINDS) study. In this clinical trial, it was found that this intervention improved the prognosis because treated patients were 30% more likely than untreated patients to have no disability [4]. The difference in prevalence estimates between the two scenarios (base conditions and treatment conditions) allowed the calculation of the amount of disability avoided and, therefore, the cost savings.

Conceptual Model

Figure 1 shows a simplified representation of the model with Arena (Rockwell, Milwaukee, WI) simulation elements. The model begins with the occurrence of a first-ever stroke. This acute event could evolve to three conditions: death, disability, or autonomy. The prognosis for patients who survive a stroke is characterized by a higher mortality risk than that occurring in the general population for two reasons. First, the risk of a recurrent stroke entails high lethality, and, second, the mortality risk from other causes is also increased. Incidence is derived from the number of first-ever strokes occurring by year in a population, and it has been estimated that these strokes represent 75% of the total number registered [2,3]. Prevalence is an instant measure defined as the number of individuals in a population who remain alive after having suffered a stroke [13]. Therefore, prevalence changes continuously through time, but we assumed that it remained constant within each year to simplify the presentation of results [13].

DES Model: Elements and Outputs

In economic evaluation, Markov models are still the standard tool to carry out cost-effectiveness analysis. They allow the calculation of the survival for each health state of a cohort according to two sets of probabilities to obtain the incremental cost-effectiveness ratios [5,21,22]. This approach is adequate when the objective is to estimate the efficiency of a new intervention. To obtain the population prevalence, however, the model must take into account all the cohorts that include living individuals with the feature of interest. We applied DES to represent the epidemiology and the clinical course of stroke in the Spanish population on the basis of other examples from the literature that use DES to represent the natural history of disease [23–26]. The main advantage of DES methods is that they can accommodate many entities with different characteristics at the same time. This flexibility enables the inclusion of all the different age cohorts contained in the population of interest. As opposed to Markov models, time flows continuously, and it is not split discretely in cycles. As the model runs and the time advances, each individual or entity experiences changes related to its attributes. These changes are recorded, and, in the end, they determine the number of incidental events and the number of entities of specific interest (disability prevalence) across time. The probability of events and the duration of processes are derived from random and independent sampling from theoretical and empirical distributions [23]. This approach permits the evaluation of thousands of entities and, therefore, assessment of the whole population of interest simultaneously. The 10th version of Arena software was used to build the model [27].

Given the epidemiologic differences, separate models for men and women were constructed. The model began with an incident cases generator that incorporated patients with first-ever stroke into the system. The incidence was reproduced through a schedule beginning in 1970 and ending in 2015. The first 30 years were the warming-up period, and the results were analyzed from 2000 to 2015. Incidental rates from hospital registers in Spain from 1995 to 2005 were used. We applied the figures from 1995 to the previous years. On the basis of the literature, we considered that 75% of all patients with stroke seen in Spanish hospitals had first-ever strokes [2,3]. The incidence from 2006 to 2015 was estimated by applying 2005 rates for sex and age to the population predictions of the Spanish Statistics Institute.

In DES, each case is called an entity. At entry to the system, each entity had to be described according to its individual attributes and the occurrence of events. First of all, age was assigned randomly according to the empirical distribution drawn from the Spanish Health Statistics Unit in association with the number of strokes by age. A Gompertz distribution was used to randomly assign time until death in function of age. The parameters of the Gompertz distribution were calculated from Spanish all-cause death rates [28], and a relative risk of 2.6 [6,7] was applied to take into account the excess mortality risk from other causes in patients with stroke. The Gompertz distribution parameters for the general population were adjusted by that relative risk to obtain the parameters for the population of patients with stroke. The formula used a random factor (u) to obtain values from probabilities and natural logarithms (Ln).

Distribution parameters appear in Table 1.

$$\text{Time until event} = \frac{1}{\beta} \times Ln\left(1 - \frac{\beta}{\alpha} \times Ln(1-u) \times e^{-\beta \times Age}\right)$$

Time until recurrent stroke is a characteristic of each patient with stroke, and it has a key role in defining the path that an entity follows in the system. The standard approach applied in Markov models passes by obtaining a probability, but in DES a time to event is needed. We also applied a Gompertz distribution