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Minimum intravenous thrombolysis utilization rates in acute ischemic stroke to achieve population effects on disability: A discrete-event simulation model

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ABSTRACT

Background: The only pharmacological treatment with proven cost-effectiveness in reducing acute ischemic stroke (AIS) associated disability is intravenous thrombolysis with recombinant tissue plasminogen activator but it's utilization rate is still low in most of the world. We estimated the minimum thrombolysis utilization rate needed to decrease the prevalence of stroke-related disability at a population level by using a discrete-event simulation model.

Methods: The model included efficacy according to time to treatment up to 4.5 h, and four scenarios for the utilization of intravenous thrombolysis in eligible patients with AIS: a) 2%; b) 12% c) 25% and d) 40%. We calculated the prevalence of AIS related disability in each scenario, using population based data. The simulation was performed from 2002 to 2017 using the ARENA software.

Results: A 2% utilization rate yielded a prevalence of disability of 359.1 per 100,000. Increasing thrombolysis to 12% avoided 779 disabled patients. If the utilization rate was increased to 25%, 1783 disabled patients would be avoided. The maximum scenario of 40% decreased disability to 335.7 per 100,000, avoiding 17% of AIS-related disability.

Conclusion: The current utilization rate of intravenous thrombolysis of 2% has minimal population impact. Increasing the rate of utilization to more than 12% is the minimum to have a significant population effect on disability and should be a public policy aim.

1. Introduction

Ischemic stroke represents 80% of all strokes and has a considerable impact on mortality and disability, especially in low and middle-income countries [1,2] Population based studies have shown that 20% to 40% of stroke survivors will have some residual disability requiring care, leading to a major burden on health systems, social services and families [3–5].

The only pharmacological treatment with proven cost-effectiveness in reducing acute ischemic stroke (AIS) associated disability is intravenous (iv) thrombolysis with recombinant tissue plasminogen activator (rTPA) [6–8]. Although this treatment is recommended in clinical practice guidelines throughout the world [9–11] its utilization rate is still very low [12]. The rate of thrombolysis in patients with AIS was 3.5% in 2008 in a population sample and 5.1% in a hospital registry in the USA in 2012. In Sweden it was 8.6% in 2010 and 8.6% in Australia. In Catalonia, 5.9% of AIS patients were treated with thrombolysis in 2007 and in Taiwan only 1.05% AIS patients received thrombolysis in 2010 [13–18]. Studies in low and middle income countries have reported even lower thrombolysis use. Only 1.5% in Pakistan [19], 1.05% in Argentina [20] and 1.7% in Chile in 2009 [21]. The main barriers to

Abbreviations: AIS, acute ischemic stroke.; rTPA, recombinant tissue plasminogen activator.; CT, computed tomography.; OTT, onset to treatment time.; mRs, modified Rankin score.

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thrombolysis utilization in AIS are prolonged time from symptoms onset to hospital arrival and minor or rapidly improving stroke symptoms [22,23]. Furthermore, although thrombolysis is efficacious and safe in older patients, advanced age may still be an exclusion criteria in some countries [24,25].

Few studies have investigated the public health impact of extending this intervention to a broader population [26,27]. Our aim was to model the population effect of increasing iv thrombolysis utilization on the prevalence of stroke-related disability.

2. Material and methods

We used a discrete-event simulation of the natural history of AIS in the Chilean population, based on the method developed by Mar et al. [28]. This model was adapted to estimate the prevalence of AIS-related disability in an adult population under different scenarios of intravenous thrombolysis utilization. The conceptual model is illustrated in Fig. 1, beginning with the occurrence of a first-ever ischemic stroke. Patients with AIS who had no severe disability at stroke onset were considered eligible for thrombolytic therapy. We used the modified Rankin score (mRs) as measure of disability after stroke [29]. The possible outcomes of AIS are death (mRs of 6), unfavourable functional outcome (mRs of 2 to 5), representing AIS-related disability, or a favourable outcome indicating total functional independence (mRs of 0 to 1). The use of intravenous thrombolysis decreases the probability of disability but not the probability of death [6]. Because the benefits of this therapy depend on the time frame from symptom onset to treatment [30], when representing the patient pathway, we included the distribution of the time from symptom onset to computed tomography (CT) confirmation of AIS and excluded patients with diagnostic confirmation beyond the 4.5-hour treatment window. Prognosis also is associated with recurrence, because case-fatality is higher in recurrent strokes. In addition, the probability of death from causes other than stroke is higher in individuals with a prior stroke than in the general population, and this probability further differs depending on the residual disability from stroke [31]. To run the simulation, we used the ARENA software, version 12. The discrete-event simulation model allowed the results of interest to be obtained depending on different scenarios of thrombolysis utilization rates. The first alternative was the current thrombolysis utilization of approximately 2%, based on a retrospective study performed in a representative sample of patients with AIS admitted to metropolitan public hospitals in Santiago, which reported that 1.7% of all patients with a confirmed ischemic stroke received thrombolysis in 2009 [21]. The second alternative was thrombolysis utilization among eligible patients who received CT-confirmation of non-haemorrhsagic stroke within the treatment window of 4.5 h or 12%. This was also based in our findings in a large representative sample of hospital in Santiago, in which 11.6% of all patients with AIS has a CT scan in this time window [21]. We chose this scenario not only because it reflects the available data in Chile on neuroimaging diagnosis in AIS within the time window, but also because it would mainly require reducing post-admission barriers to the utilization of thrombolysis and represents approximately the utilization rate in high stroke volume populations with well-organized medical systems. The third alternative involved thrombolysis utilization in 25% of eligible patients with confirmed AIS, which would involve not only reducing post-admission barriers, but also reducing pre-admission barriers to thrombolysis utilization [32]. Finally, we formulated a fourth alternative consisting of a hypothetical scenario of higher utilization, assuming that 40% of patients with AIS receive diagnostic confirmation within the therapeutic window and are eligible and are treated with thrombolysis.

2.1. Model parameters

To incorporate the probabilities and time to events in the model, we used theoretical and empirical distributions (Supplemental data). The characteristics or attributes of the individuals simulated on entry to the system (incidence) were sex, age, and disability at stroke onset. Age and sex were assigned on a probabilistic basis, using data extracted from the registries of Chile's National Institute of Statistics and on the distribution of incident cases of a first-ever stroke in the PISCIS study stratified by age and sex [4]. This community-based incidence study performed in Chile between 2000 and 2002 reported a standardized incidence rate of acute ischemic stroke of 66.5 (95% CI 56.9; 76.1) per 100,000 inhabitants (mean age, 66.4 years [SD 14.9]; 56% men). Given that not all patients with a confirmed ischemic stroke are eligible for thrombolysis [25], individuals with severe disability before stroke

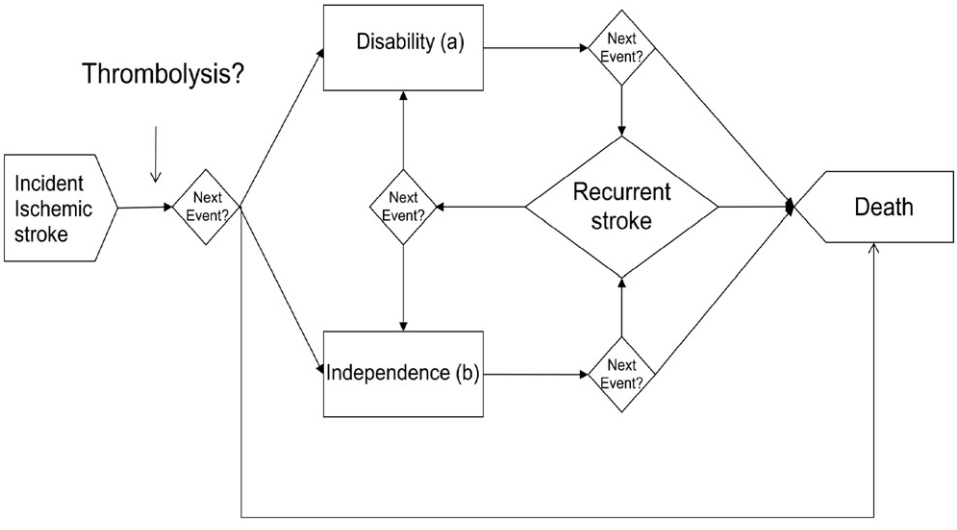

Fig. 1. Flow chart representing the natural history of stroke.

onset were not included since they would derive no benefit, reflecting clinical judgment in the indication for intravenous thrombolysis. To include this criterion and to randomly assign this attribute to incident cases, we used data corresponding to the age and sex distribution of severe disability extracted from the 2009 Chilean National Socioeconomic Characterization Survey [33].

The disability-reducing benefit of intravenous thrombolysis depending on stroke onset to treatment time (OTT) was incorporated into the model by using the results of a meta-analysis performed by Lees et al. [34]. We included the proportions of patients with a favourable outcome (modified Rankin Score 0 to 1) stratified by OTT ranging from 90 min to 270 min. Individuals in the system are subject to two competing and mutually exclusive risks (death and recurrent stroke). Time to death from any cause was included in the model using the official records of deaths and population of Chile. On the basis of the estimates of Slot et al. [31], we included a relative risk for all-cause mortality of 1.52 among patients with a favourable outcome (mRs 0–1) and of 2.88 among those with unfavourable outcomes (mRs 2–5). Health outcomes after a recurrent stroke were estimated on the basis of a study performed in Spain [28]. The data used in our model was 23% of recurrent strokes from the total number of ischemic strokes found in the PISCIS community study performed in Chile [4].

2.2. Health care organization and provision of thrombolysis in Chile

Chile has a mixed public and private health system. The public health system provides care for roughly 80% of admitted patients and hence stroke. There are national stroke care guidelines provided by the Ministry of Health for the care of acute ischemic stroke and an explicit list of guaranteed minimal management interventions, that include hospitalization, CT scan and neurological consultation for all patients [35]. Thrombolysis is paid for to the hospitals providing it by the public health fund (FONASA), and is being increasingly utilized in large regional hospitals in the country as part of the implementation of the National Stroke Plan [36].

2.3. Analysis

The simulation time horizon spanned from 2002 to 2017. We validated the model by comparing the outputs with the parameters associated with the epidemiology of stroke in Chile and other countries [3,37,38]. The results rendered by the model were the number of patients receiving thrombolysis, the prevalence of AIS-related disability and the total prevalence of stroke by year simulated, depending on the level of thrombolysis use. Prevalence rates for stroke and for AIS-related disability were stratified by age and sex, using data from the Chilean population published by the Chilean National Statistics Institute. Age-standardized rates for each year were calculated using Segi's World population. To determine statistically significant differences among the scenarios in the sensitivity analysis, a calculated sample size of 100 replications was considered sufficient. The criterion for halting each replication was reaching the end of the simulation horizon (year 2017).

The ethics committee of Facultad de Medicina, Universidad Mayor approved the study protocol.

3. Results

The results of the simulation revealed a mean (SD) age of 66.2 (12.7) years for men and 70.4 (14.5) for women. Life expectancy of patients with a first-ever ischemic stroke that resulted with the simulation decreased with increasing age of stroke occurrence. When the first stroke occurs at 50 years, life expectancy in men was 13.6 years and 15.0 years in women. Survival was reduced to 9.7 and 9.4 years respectively, when the event occurs during the 6th decade of life. In the elderly, women had a lower life expectancy than men. At age 70, life expectancy was 5.9 years for men and 5.7 for women. At 80 years, life expectancy was 3.6 and 3.1, respectively. Based on the current thrombolysis utilization rate, the age-standardized prevalence of ischemic stroke was 550.1 per 100,000 inhabitants in 2017 (Table 1). In all age groups, prevalence rates were higher in men than in women throughout the time horizon (Supplemental data). When stratified by age, prevalence was clustered between the ages of 65 and 74 years, followed by the age group 75 to 84 years. The age-standardized AIS-related disability prevalence was 279.1 per 100,000 inhabitants, corresponding to approximately 50% of the total number of prevalent cases of stroke (Fig. 2).

For the 2002 horizon of the simulation, the total incident cases of first-ever stroke were 11,750 and at the end they were 15,100. For the 2017 horizon the model rendered only 225 thrombolysed patients with the current usage scenario and 5230 for the 40% utilization scenario. If the current thrombolysis use was maintained, there would be 51,680 survivors with disabilities in 2017. Under the second scenario, 50,982 persons would be disabled, 49,897 under the third scenario, and 48,304 would be disabled under the highest utilization scenario, respectively (Table 1).

Fig. 3 shows the age-adjusted prevalence rate for AIS-related disability according to the different thrombolysis utilization scenarios for the entire adult Chilean population. Throughout the simulation horizon, the decline in the prevalence rate of AIS-related disability was most pronounced in the second, third, and fourth thrombolysis utilization scenarios compared with the alternative of maintaining the current utilization scenario of 2%. In 2017, and under the current thrombolysis utilization rate, the estimated AIS-related disability rate was 359.1 per 100,000 inhabitants, equivalent to 51,680 cases; this decreased to 354.3 for the utilization rate of 12%, to 347.7 for the utilization rate of 25% and to 335.7 per 100,000 inhabitants for the highest utilization rate scenario.

The simulation showed that increasing the current thrombolysis utilization rate of 2% to 12% of eligible patients would prevent 779 cases of AIS-related disabilities in 2017, representing 2% of survivors disabled after AIS. When this figure was increased to 25% of patients with ischemic stroke, the number of cases of disability avoided compared to current thrombolysis utilization throughout the simulation horizon ranged from 102 in 2002 to 1783 in 2017, representing 3% of disabled survivors after a first-ever stroke for the last simulated year. If 40% of eligible patients received thrombolytic therapy, a total

Table 1
Descriptive results of simulation by selected years.

	2002	2005	2010	2015	2017
Incidence of ischemic stroke	11.750	12.800	13.925	14.800	15.100
Number of patients if thrombolysis is 2%	176	183	200	224	225
Number of patients if thrombolysis is 12%	1356	1439	1565	1645	1758
Number of patients if thrombolysis is 25%	2857	3102	3392	3622	3736
Number of patients if thrombolysis is 40%	4611	4813	5027	5161	5230
Disabled patients if thrombolysis is 2%	44.320	45.132	47.795	50.674	51.680
Disabled patients if thrombolysis is 12%	44.358	44.909	47.182	49.860	50.982
Disabled patients if thrombolysis is 25%	44.218	44.595	46.541	48.915	49.897
Disabled patients if thrombolysis is 40%	44,040	43,860	45,205	47,268	48,304

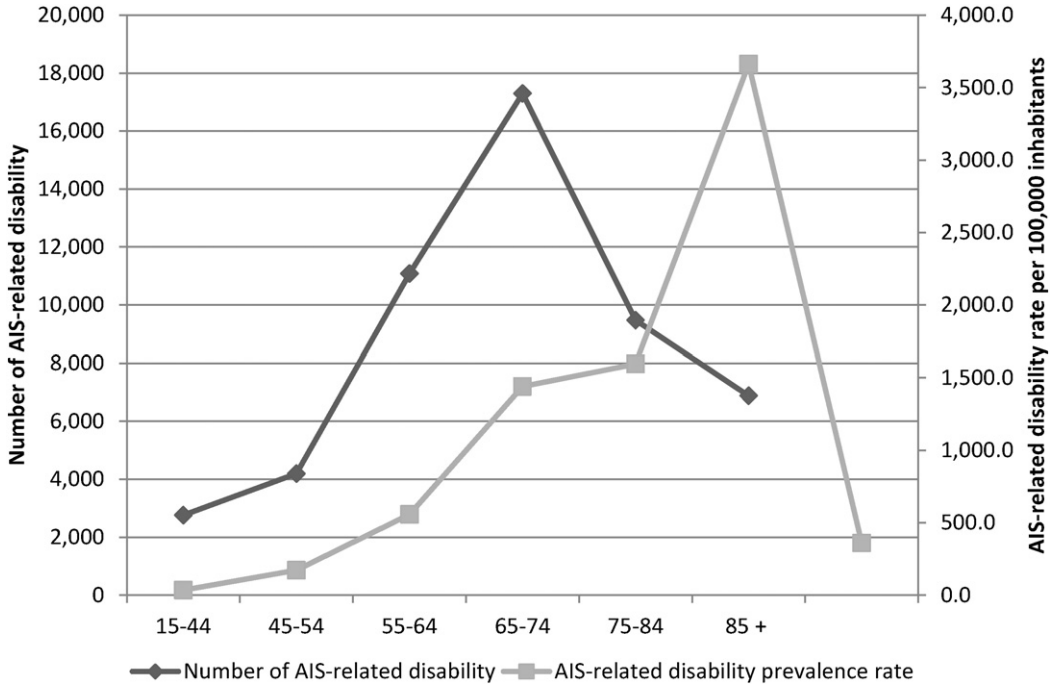

Fig. 2. Acute ischemic stroke related disability by age groups in the Chilean population in the year 2017 based on discrete event simulation model.

of 4264 cases of AIS-related disability would be prevented in 2017, corresponding to 8.8% of the total number of persons with disability (Fig. 4).

4. Discussion

The main finding of this study is that increasing thrombolysis utilization to 12%, 25% or to 40% of patients with ischemic stroke in this population would significantly reduce the prevalence of AIS-related disability at a population level. The first scenario, with almost anecdotic use of thrombolysis, corresponds to current use in metropolitan public hospitals in Chile, a proportion similar to that found in middle and low-income countries worldwide as well as community and non-academic medical centres [39,40]. The results show that, if this scenario is unchanged, iv thrombolytic therapy will have minimal effect at the population level in preventing AIS-related disability; consequently isolated efforts would be doubly ineffective from the public health perspective, because they would have no population benefit but would still carry the inherent risk of thrombolysis of producing haemorrhage and the cost of setting up the procedure in limited emergency rooms and stroke units. The second scenario represents a realistic goal for many health care systems, consisting of administering thrombolysis in eligible patients with CT-confirmation of stroke within the treatment window; that is, this scenario implies an improvement in the organization of the health provision to reduce door-to-needle times by implementing stroke codes [32]. The third and fourth scenarios involve a more ambitious goal in which one out of every four eligible patients and 2 out of 5 patients with ischemic stroke would receive iv thrombolysis. Reaching this goal involves both hospital and community-based interventions to achieve earlier presentation to hospital or the emergency department by patients and their caregivers, as well as other measures to reduce barriers in access to iv thrombolysis in ischemic stroke. In many countries iv thrombolysis is provided by national health systems as part of national stroke programs [41]. However, minimum utilization goals have not yet been defined as a policy objective in health care system [42]. The underutilization of iv thrombolysis in the real world is a public health concern and practical policies need to be put in place to overcome the known barriers to its implementation, especially unawareness of stroke symptoms by the population and hence delays in consultations to emergency departments, lack of stroke codes in many emergency settings and inappropriate infrastructure or organizational support including lack of quality improvement programs [32,43].

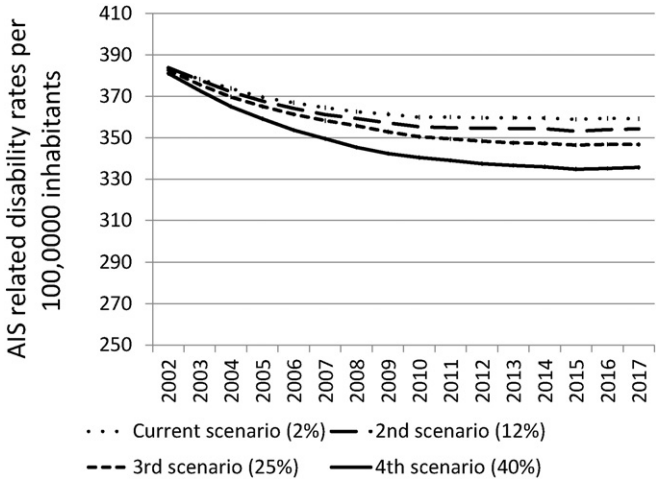

Fig. 3. Acute ischemic stroke related disability rate per 100,000 inhabitants by thrombolysis utilization scenario and simulation year.

Other studies that have simulated the population impact of iv thrombolytic therapy have reported favourable but modest results of increased utilization. Mar et al. applied discrete-event simulation in the Spanish population; among a total of 101,270 stroke events, thrombolysis use in 10% of eligible patients would prevent 4031 cases of stroke-associated disability, representing 3% of the total number of persons with stroke-related disability [28]. The findings for our sample population show that use of this treatment in 12% of eligible patients would avoid AIS-related disability in 2% of stroke survivors in 2017. Another study performed in the UK that applied discrete-event simulation to evaluate the cost-effectiveness of increasing the use of intravenous thrombolysis concluded that a provision of 50% was cheaper than a provision of 10%, implying a moderate increase in QALYs per every clinically suitable patient [26].

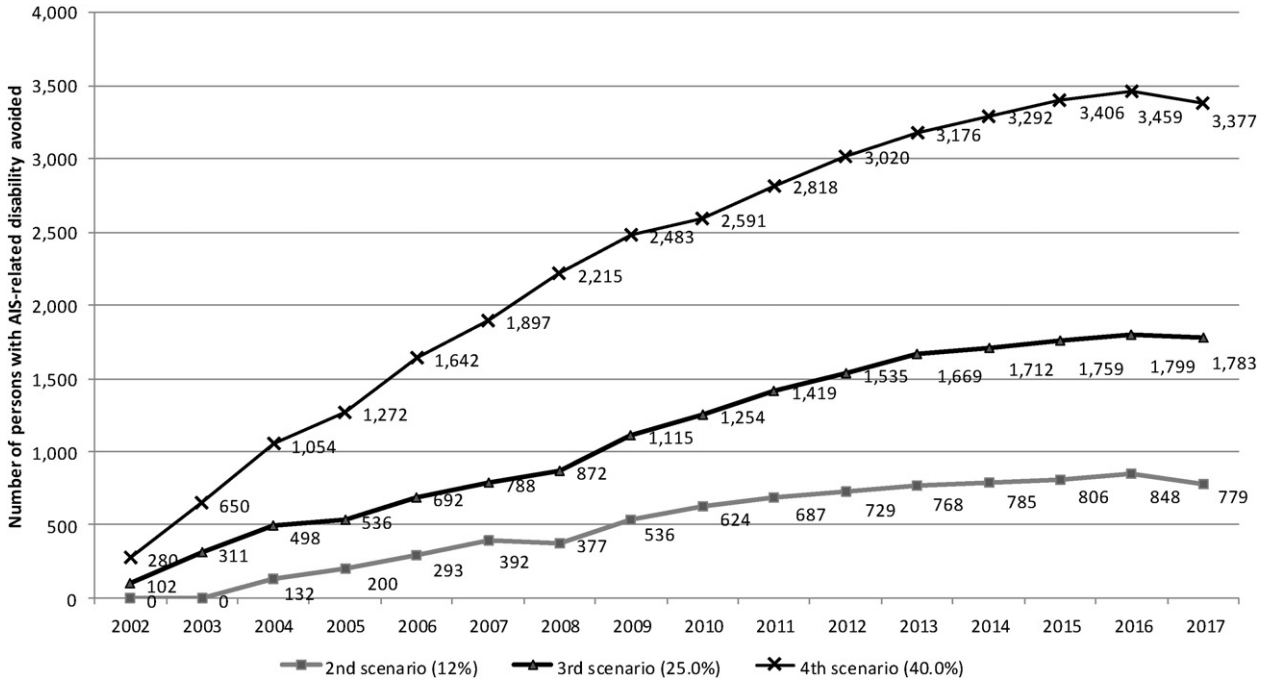

Fig. 4. Number of persons with stroke-related disability avoided, according to thrombolysis utilization scenarios compared with current utilization of iv thrombolysis.

Our results show that the model is accurate as it adequately reproduced the epidemiology of stroke in the Chilean population reported in the community based PISCIS study a decade ago. We estimated that half of all survivors of ischemic stroke would have some degree of AIS-related disability in 2017. In the Basque Country in Spain, the age-standardized stroke-related disability prevalence rate estimated for 2000 was 208 per 100,000 inhabitants, representing 40% of the total number of prevalent cases in all types of stroke. In Auckland, Bonita et al. reported that approximately 461 per 100,000 inhabitants had residual disability after some type of stroke in 1991–92, estimating an age-standardized stroke prevalence of 833 per 100,000 inhabitants [37]. One of the reasons for the differences between the Spanish and New Zealand studies and our own, is that the former included haemorrhagic strokes and subarachnoid haemorrhages, while ours included only ischemic stroke. The magnitude of our estimation of stroke-related disability is slightly higher than the results reported by Ferri et al. using population-based surveys in distinct low- and middle-income countries [3].

Strengths of this study are that our conceptual, epidemiological and statistical model incorporates data from more recent clinical trials and meta-analysis of iv thrombolysis, such as the extension of the therapeutic window for thrombolysis to 4.5 h and inclusion of those aged 80 and more [34]. The latter is a key issue because of population aging in many countries and increasing number of patients over 80 presenting with acute ischemic strokes in the emergency rooms. Another interesting feature of this study is the incorporation of data sources such as incident cases of ischemic stroke from a well performed population-based study. In addition, this study takes into account, as a comparative scenario, the current thrombolysis utilization rate based on a study performed in a probabilistic sample of patients with AIS of several public hospitals in Santiago, Chile, whose magnitude is comparable to those reported in countries with similar socioeconomic characteristics. Finally, this study integrates time to treatment, which is the main barrier to the use of thrombolytic therapy, incorporating the timeliness of treatment in disability outcomes in the model.

Our study has several limitations. We did not include the distribution of patient-level factors that are contraindications to thrombolysis use because we lacked the necessary information sources at a population level. However, we considered the joint effect of contraindications to thrombolysis in the choice of alternative utilization scenarios. Another limitation was the impossibility of distinguishing among distinct grades of AIS-severity, to incorporate in the model. The generalizability of the results of this study to different countries is a limitation of our study and should be kept in mind particularly because all of the data come from population and hospital based data from Chile. This is very important because the implementation barriers to iv thrombolysis in Chile may be different from other countries with diverse organizational and clinical settings. Furthermore, we did not calculate the costs of increasing utilization rates from 2% to 12% or more, but this was investigated by Barton et al. in the UK where they demonstrated that increasing thrombolysis from 10% to 50% of eligible persons, decreased total cost per patients particularly by less spending in community rehabilitation costs and in institutional care [26].

5. Conclusion

In conclusion, we found that an increase in thrombolytic therapy to 12% or more reduces ischemic stroke related-disability at a population level. Based on our results, we recommend that a goal of more than 12% utilization is set as a performance standard for iv thrombolysis as a public health policy aims in stroke management, and specific programs to lower barriers to iv thrombolysis use in acute ischemic stroke be implemented.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jns.2016.04.005.

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