

Systematic Review on economic and managerial analysis of stroke

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Abstract

Background. Stroke is the third leading cause of death after acute myocardial infarction and cancer, the leading cause of disability and the second cause of dementia, resulting in considerable social and economic costs.

Objective. This review of literature, starting from the awareness of the substantial negative impact of stroke in Italy, both clinically and economically, has the main objective of highlighting the economic assessment of preventive strategies that is the assistance routes provided for patients affected by stroke.

Methods. A literature review was conducted using two electronic medical journal databases: Scopus and PubMed. The presentation of the results is in compliance with the PRISMA method.

Results. In this review process, following the above detailed selection a total of 15 articles were selected, all meeting the inclusion criteria. Of these, 4 are in Italian and 11 are in English. Twelve articles were published between 2009-2014, two in 2007 and one in 2015. Eleven articles performed cost analyses and economic assessments taking as reference only Italian cases while the other articles considered an Italian context together with that of other Countries.

Conclusions. The final result to be achieved is to increase the quality of health care assistance, mainly through interventions aimed at reorganizing the assistance approaches, without excessive additional costs, but rather creating quantifiable savings in terms of reduction in beds needed to assist in case of stroke events and, as a result of minor disability and dependence, in terms of reduction of rehabilitative, assistance and social expenditures in the long term.

Keywords: Stroke costs; Economic evaluation; Cost-effectiveness; Management.

Introduction

Acute cerebrovascular disease is, in industrialized countries, the third leading cause of death after acute myocardial infarction and cancer (causing 10-12% of all deaths per year), the leading cause of disability and the second cause of dementia, resulting in considerable social and economic costs (Sarti et al, 2000).

More than 196,000 strokes occur annually in Italy, of which about 80% are new cases and 20% are relapses (ISTAT, 2015). 75% of strokes affect subjects beyond sixty-five years of age. The incidence increases steadily with age, reaching the highest levels in subjects over the age of eighty five years.

The prevalence rate of stroke in the Italian population with age between 65 to 84 years is equal to 6.5%, and is slightly higher in men (7.4%) than women (5.9%) (ISTAT, 2005; Amaducci et al, 1997; Di Carlo et al, 2003); the significant aging of the population will lead in the future to an inevitable increase in cases.

Stroke affects, to a lesser extent, young people and it is estimated that every year the number of people in productive age (<65 years) affected by stroke is around 27,000 (ISTAT, 2015). Ischemic stroke is the most common form of stroke (80%), while intraparenchymal hemorrhages are present at a rate of 15-20% and sub arachnoid hemorrhages represent about 3% of the cases (Sudlow et al, 1997).

The acute mortality (within 30 days) after stroke is equal to approximately 20% while that within 1 year is equal to about 30%; the (intraparenchymal and sub-arachnoid) hemorrhages have higher early mortality rates (30% and 40% about after the first week, 50% and 45% after 1 month) (Di Gianfilippo et al, 2006). After one year from the onset of an acute event, about a third of stroke survivors, regardless of whether it is ischemic or hemorrhagic, presents a high degree of disability, so that they can be defined fully Dependents.

Therefore, due to its high incidence and high risk of permanent disability, stroke is welfare, rehabilitative, social and large economic problem, representing 2-4% of the total health expenditure in developed countries (Evers et al, 2004).

In addition, the cost of stroke treatment is growing. According to the latest estimates available at the European level, Europe will spend each year from 72 billion to 183 billion Euros only to treat people affected by stroke (Nichols et al, 2012).

Specifically for Italy, an annual health expenditure of over 2.7 billion Euros is estimated. These direct costs must be added to the indirect costs of "informal treatments" in the amount of 1.5 billion Euros and the loss of productivity caused by years of life prematurely lost and related disability. The latter costs amounted, for Italy, to about 392 million Euros for loss of productivity and over 45 million Euros for disability (Nichols et al, 2012).

This systematic review of literature, starting from the awareness of the substantial negative impact of stroke in Italy, both clinically and economically, has the main objective of highlighting the economic assessment of preventive strategies that is the assistance routes (treatment and rehabilitation) provided for patients affected by stroke.

For this purpose, the different treatment strategies of the last ten years were analyzed, leveraging from approaches that can provide positive results in terms of clinical effectiveness and economic return.

Materials and methods

A literature review was conducted using two electronic medical journal databases: Scopus and PubMed.

The presentation of the results is in compliance with the PRISMA method for presentation of systematic reviews.

- Article selection

The keywords used were "stroke", "cost effectiveness", "cost utility", "cost benefit", "cost" and "Italy". Combined searches were carried out for: "Stroke AND cost effectiveness AND Italy", "Stroke AND cost utility AND Italy", "Stroke AND cost benefit AND Italy" and "Stroke AND cost AND Italy".

- Reference time period

A time restriction was applied to the research carried out; in fact, only the articles published in the last ten years were considered: from 2006 (included) to 2015 (included).

- Inclusion criteria

Pertaining to the Italian situation, the following were included:

- Articles or reviews related to economic assessments on stroke and related health treatment;
- Articles or reviews concerning the economic burden of stroke and its temporal changes;
- Articles or reviews regarding the strategies and/or action plans on stroke and related economic impact.

- Exclusion criteria

Starting from the moment of title selection, the following were excluded:

- Articles or reviews published in a language other than Italian and/or English;
- Articles or revisions that do not consider Italy;
- Articles or reviews that analyze the stroke problem only from a clinical point of view, but neglect the economic aspect;
- Articles or reviews that do not clearly meet the research subject and its purpose.

- **Data extraction and quality assessment**

After completion of bibliographic research, two authors independently examined the list of titles and then the abstracts, and then their full-text to include those that met the inclusion criteria. A third author was involved in the event of disagreement between the first two.

Results

In this review process, following the above detailed selection (diagram 1), a total of 15 articles were selected, all meeting the inclusion criteria.

Of these, 4 (Capri et al, 2013; Lucioni et al, 2010; Ravasio et al, 2014; Scaletti et al, 2014) are in Italian, while the remaining 11 (Bottacchi et al, 2012; Carinci et al, 2007; Cesaroni et al, 2009; Fattore et al, 2012; Häkkinen et al, 2015; Hays et al 2006; Hurst et al, 2007; Mahoney et al, 2010; Masiero et al, 2014; Mureddu et al, 2013; Piscitelli, 2012; Schuetz et al, 2013) are in English.

From a timing standpoint, twelve articles out of the selected fifteen, or 80%, were published between 2009 and 2014 (Bottacchi et al, 2012; Capri et al, 2013; Cesaroni et al, 2009; Fattore et al, 2012; Lucioni et al, 2010; Mahoney et al, 2010; Masiero et al, 2014; Mureddu et al, 2013; Piscitelli, 2012; Ravasio et al, 2014; Scaletti et al, 2014; Schuetz et al, 2013) , while two in 2007 (Carinci et al, 2007; Hurst et al, 2007) and only one in 2015 (Häkkinen et al, 2015); no article was published in 2006 and 2008, in the three-year period included in the review analysis.

Finally, eleven articles (Bottacchi et al, 2012; Capri et al, 2013; Carinci et al, 2007; Cesaroni et al, 2009; Fattore et al, 2012; Lucioni et al, 2010; Masiero et al, 2014; Mureddu et al, 2013; Piscitelli, 2012; Ravasio et al, 2014; Scaletti et al, 2014) performed cost analyses and economic assessments taking as reference only Italian cases while the other four articles considered an Italian context together with that of other European countries and the U.S.A., (Häkkinen et al, 2015; Hurst et al, 2007; Mahoney et al, 2010; Schuetz et al, 2013).

The agreement among the authors for the selection of the title was high ($\kappa = 90\%$); and the one for the assessment of the full-text ($\kappa = 100\%$) was unanimous.

The table 1 schematically shows the articles selected and included in the review, subdividing them by title, year, author and key concepts. The order of presentation is chronological, from most recent to oldest.

Observations & Managerial Implication

The content analysis of the 15 articles selected in accordance with the leading international review analyses is summarized in Table 2 which shows the information provided by those Articles; in this regard, each table shows the study design, the population being assessed, the economic assessment technique used and the main results obtained.

Two main observations emerged from the review study on which the literature showed particular interest:

- I. The most widely used economic evaluation technique was the Cost-Effectiveness one.
- II. The most assessed stages were the preventive stage and the stage related to patients affected by stroke.

Concerning the first point, it is necessary to clarify that until a few decade ago, the introduction of a new pharmaceutical drug, a new piece of equipment, a new method, an innovative management model, and in summary, the introduction of new health care technology to be understood in the broadest sense of the term, was subjected exclusively to clinical judgment aimed at verifying its safety and efficacy. Later, the lack of resources available associated with the cost increase of health

services in general, and in particular to the significant increase in costs due to the adoption of technological innovations, generated the need to support clinical judgment also from an economic stand point to guide the choice of the policy-makers among all the alternatives available towards the most effective and efficient one.

The review analysis showed that in relation to stroke in seven articles out of the fifteen selected, the economic assessment technique used is that of Cost Effectiveness (Capri et al, 2013; Mahoney et al, 2010; Lucioni et al, 2010; Masiero et al, 2014; Mureddu et al, 2013; Ravasio et al, 2014; Schuetz et al, 2013). For this purpose, it must be specified that often in literature the terms "cost-effectiveness analysis" and "cost-utility analysis" are used with great flexibility and they are sometimes seen as interchangeable terms since the difference between the one and the other methodology is limited to one particularistic aspect that is whether an adjustment for quality of life had been included or not; in fact, some of the reviewed sources, despite affirming of having conducted a CEA (Cost effectiveness analysis), presented their results as QALY, adhering more to the definition of Cua (Lucioni et al, 2010; Mahoney et al, 2010; Ravasio et al, 2014; Schuetz et al, 2013).

That said, the motivation supporting the first observation that emerged, explains that Cost Effectiveness analyses are the most suitable and efficient for economic and health sector assessments because they bypass the controversial stage of monetization of costs and benefits in the sector, the nature of which is often "intangible" (think of quality of life, of time value, at the same level of health/disease, etc.), called for, instead, by a cost-benefit analysis. Also, if at the beginning one could argue that Cea only assesses the results of the various alternatives in terms of quantity, ignoring the changes that could also occur in qualitative terms through the adoption of Qaly, the limit is exceeded.

What is stated above is even more significant when trying to assess from an economic stand point a more efficient rehabilitative and organizational health strategy (Masiero et al, 2014), or a more effective medicine (Masiero et al, 2014), o un farmaco maggiormente efficace (Capri et al, 2013; Mahoney et al, 2010; Lucioni et al, 2010; Ravasio et al, 2014), or a suitable preventive action (Mureddu et al, 2013; Schuetz et al, 2013) for a disease such as stroke, which can cause disabling situations that have a major impact not only on the length of life, but also on its quality.

That said, the additional four articles present an estimative approach to cost analysis, in confirmation of the need to propose new health technologies capable of limiting the economic burden that this disease has on the NHS (Bottacchi et al, 2012; Fattore et al, 2012; Piscitelli, 2012; Scaletti et al, 2014). Obviously these analyses, although mainly concentrated on the need to achieve cost reduction, assume the presence of pharmaceutical drugs and rehabilitation and health care options that imply a health efficiency increase; the objective to protect and improve health remains the fundamental base of any economic study in the health sector.

It is no coincidence that the review study highlighted two works that apply a socio-economic assessment, even though with totally different perspectives; the first one focuses on resource allocation and on the organizational model of the health care system planned for stroke in order to increase the performance of one of the main services for society (Hurst et al, 2007); the other one analyses the incidence differences and their economic impact in the different socio-economic segments of the population, in order to identify the segment to which the policy-maker should pay more attention (Cesaroni et al, 2009).

Moreover, an article in order to meet the research objective makes use on an efficacy or effectiveness assessment. In fact, a cost assessment and the whole economic aspect play a marginal and consequential role compared to the desire to estimate a reduction in mortality risk, and, therefore, a "clinical" factor (Carinci et al, 2007).

Finally, a last source included in this work carries out a cost-quality analysis that is a hybrid technique between a Cea and a Ca (Cost analysis) since it considers the quality parameters, instead of those related to efficiency and utility, and compare them with the respective costs in order to identify the health strategy, which often leads to the delivery of a service with a greater level of cost/quality (Häkkinen et al, 2015)..

The second observation that emerged from the review analysis was related to the pathology stage on which the review of the fifteen sources of literature was mainly focused. This allowed identifying the main contributions that scientific research provided according to the choices of health policy makers in Italy in the field of stroke. Six articles are dedicated to the preventive stage of stroke in Italy (Bottacchi et al, 2012; Capri et al, 2013; Cesaroni et al, 2009; Mureddu et al, 2013; Ravasio et al, 2014; Schuetz et al, 2013), the same number of articles paid attention to the management and treatment of patients affected by stroke (Fattore et al, 2012; Häkkinen et al, 2015; Hurst et al, 2007; Lucioni et al, 2010; Mahoney et al, 2010; Scaletti et al, 2014), and only three articles concerned the period of rehabilitation of people affected by stroke (Carinci et al, 2007; Masiero et al, 2014; Piscitelli, 2012).

Given that stroke in Italy represents the third leading cause of death and the first cause of disability, affecting each year about two hundred thousand people, ten thousand of them in highly productive age also from the economic standpoint, adequate prevention becomes critical to limit the social health impact of this disease, otherwise devastating.

Prevention is, of course, an approach to take also in order to simultaneously limit the resulting economic impact, which, as previously highlighted, in Italy is estimated to be an annual health expenditure of over 2.7 billion Euros (Nichols et al, 2012). Therefore, it is hardly surprising that much of the reviewed literature performs estimative analyses in this light to propose new health technologies capable to pursue jointly and collaboratively both public health objectives and economic ones.

It is interesting to note that in our country stroke prevention is faced from different points of view, confirming that it is necessary to undertake such a way to contain upstream its clinical and economic problem. From a pharmacological point of view, in light of the national health system, rivaroxaban (Capri et al, 2013) and dabigatran (Ravasio et al, 2014) are assessed, and both are cost-effective and thus able not only to bring benefits in terms of health by reducing incidence, but also by leading to a potential decrease in costs for the National Health System. The related two sources that were reviewed contributed greatly to the approval of the two drugs by the EMA (European Medicines Agency) and certainly imply the willingness to pursue reimbursement by the AIFA (Italian Drug Agency) to bring into real terms what was demonstrated by the research.

Another way in which this issue is approached is the will to find a high-performing health strategy that limits the occurrence of new episodes or relapses. In this regard, the literature indicates how such a result is reachable both directly, perhaps by selecting among the various Health Check Strategies the best in terms of cost-efficacy (Schuetz et al, 2013), and indirectly through the choice of a strategy that promptly identifies asymptomatic left ventricular dysfunction (Mureddu et al, 2013) which, although moderate, is independently associated with an increased risk of ischemic stroke and related increase in costs that the pathology involves (Hays et al, 2006).

Linking back to the first observation, it is no coincidence that in the evaluation of pharmacological proposals and preventive health strategies, the technique of cost effectiveness was adopted; in fact, this allows highlighting that an adequate preventive program for stroke would improve simultaneously both the level of population health and the management of resources of the national health system.

The other two sources deal with prevention in terms of its promotion, aiming at pointing out additionally the importance that this stage could, and should, have in a tangible attempt both to reduce the direct and indirect costs that stroke represents for Italian health system and for society, and to improve health overall. In fact, the first, through a cost analysis, estimates the amount of costs in a three-year period following the first stroke event to conclude specifically with the need to promote a high-performance preventive activity as a major opportunity to reduce that burden (Bottacchi et al, 2012); the second, after identifying the socioeconomic class that demands more resources from the NHS, and at the same time continues to require them, focuses its attention on the promotion of prevention for a social standpoint to optimize the allocation of the resources (Cesaroni et al, 2009).

The review analysis showed the ability to achieve considerable benefits through prevention and related need for the Italian Health Care System to invest in it. It also made clear, as a very important factor, the evaluation and proposal of management and treatment models for patients affected by stroke so as it is possible to limit the wide disabling complications, any relapses and to pursue an improvement in the quality of life of these subjects. Obviously this would consequently involve benefits in economic terms. Even in this case, contribution offers appear differentiated among pharmacological, managerial-organizational and socio-health strategies.

The drugs proposed in the above two studies, Prasugrel (Mahoney et al, 2010) and Alteplase (Lucioni et al, 2010), through a cost effectiveness assessment, which as already specified is the most appropriate for assessments especially in the pharmacological industry, are identified as dominant therapies in the treatment of patients affected by stroke for their ability to limit the occurrence of complications and relapses; the first since 2014 and second since 2013 were marketed in Italy as a confirmation of the importance of the research carried out.

The other four articles that were reviewed and that approach this theme outline very well the management of patients affected by stroke in Italy with related issues and prospects for improvement. In an interview conducted with specialists of the sector, an inefficient allocation of resources was highlighted along with an organizational and managerial network that from the hospitalization of the patient up to the rehabilitation stage is marked by several critical issues that are accentuated especially in southern Italy (Hurst et al, 2007). However, at the same time, it was demonstrated how there is the possibility to invest to improve the performance of the health sector in this area because, unlike other diseases, an increase in the level of health services quality, especially in hospitals, does not involve an increase of relevant costs (Häkkinen et al, 2015). The literature also provides the most efficient ways to pursue optimization in the management of patients affected by stroke, focusing on the importance of informal care and in adopting an appropriate infrastructure suitable to ensure adequate support for such individuals (Fattore et al, 2012). Specifically at the infrastructure level, a key role would be played by the implementation of stroke units capable not only to minimize the consequences of the stroke ensuring greater patient autonomy and, therefore, a reduced demand for subsequent treatments and welfare services, but also generate savings of considerable costs for the NHS in the short term (Scaletti et al, 2014). Although the Ministry of Health seems to have understood the evidence produced by the literature, estimating the number of stroke units necessary for the whole country in the quantity of 300, to date, unfortunately, less than 170 units are operational and those that are, are mainly located in Northern Italy. Hence, the importance of urgent action to address this structural deficiency, especially in the Center-Southern regions of Italy.

Finally, an additional aspect addressed by the literature in relation to the health economic assessment is the rehabilitation. It is specifically one of the sources reviewed that emphasize the importance of rehabilitation of patients affected by stroke both in clinical terms and especially in economic ones. In fact, through a comparison of the costs of the same stage for other pathologies it is highlighted how significant the burden is for the NHS, and it is necessary to create a more efficient and effective management in this respect (Piscitelli, 2012). In recent years, the average rehabilitation time within hospitals, to limit the economic burden was greatly reduced, from 6 months to about 45 days, but this solution transferred the social and economic costs on patients and their families or on society. It seems clear that the road taken cannot represent an efficient health policy at all, so much so that thanks to high performance rehabilitation, it is possible to obtain a reduction in mortality and cost savings (Carinci et al, 2007). The last source, in this regard offers as a cost efficient technology option robot-assisted treatments and points out that an investment in this health care alternative for the rehabilitation of patients affected by stroke would be more than justified by the positive results in the medium term both on the quality of life and in terms of cost reduction for the NHS (Masiero et al, 2014).

Conclusions

Stroke in Italy, as well as in the rest of the world, represents an health matter of major importance not only from the point of view of health care assistance, rehabilitation and social assistance, but also from an economic standpoint (Evers, 2004; Nichols et al, 2012). Despite the progress of treatment, stroke remains a devastating disease, a major cause of morbidity and mortality, and one of the most costly diseases to be treated. Stroke costs are a significant drain for the Italian economy, and since the population ages, it is expected that the economic burden of the disease will increase. In this regard, the literature reviewed has shown particular interest in the economic assessment of various health strategies to reduce the burden of the disease on the budget of the various health systems, such as, for example, the use of drugs or equipment for therapeutic use (Capri et al, 2013; Lucioni et al, 2010; Mahoney et al, 2010; Masiero et al, 2014; Ravasio et al, 2014).

The type of analysis mainly used was the Cost Effectiveness analysis as a demonstration of the importance given to the incremental costs arising from health technologies introduced to contain the debilitating effects of strokes.

As it is clear from the results obtained, reducing the stroke impacts is substantial and it is necessary to implement strategies that improve the prevention and management of the disease to reduce both the incidence and prevalence of the phenomenon.

Among these, for example, are the benefits obtainable through admission to SU, which can also be realized regardless of the introduction of special treatments and are attributable to the competence of the healthcare personnel, complications prevention, prevention measures of relapses and early rehabilitation programming (Scaletti et al, 2014).

There is awareness that this problem calls for, in the first instance, a reshaping on its organization, in the sense of optimizing the use of human resources. The final result to be achieved is to increase the quality of health care assistance, mainly through interventions aimed at reorganizing the assistance approaches, without excessive additional costs, but rather creating quantifiable savings in terms of reduction in beds needed to assist in case of stroke events and, as a result of minor disability and dependence, in terms of reduction of rehabilitative, assistance and social expenditures in the long term (Carinci et al, 2007; Häkkinen et al, 2015; Scaletti et al, 2014).

It was also clear that, in order to reduce mortality and disability, the problem is not limited to the acute stage, where thrombolytic treatment plays a major role, but it should be seen in a global perspective that originates from the recognition of the first symptoms of the cerebrovascular event, and calls for the activation of local emergency services, the identification and alerting of the appropriate structures to treat the specific case, hospital management, rehabilitative treatment project, secondary prevention, the desirable return home, the acceptance of the person affected by stroke by a general practitioner (MMG), territorial specialist or an integrated home care assistance service.

The review highlighted that the decision-making process for stroke management is complex and changes considerably from country to country. There is the need for further assessments compared to current procedures used to test the economic impact of new technologies both from a therapeutic/rehabilitative point of view and from a preventive one.

Therefore, it is necessary to identify and configure the approaches and processes of treatments that are efficient, effective, achievable, verifiable and consistent because only in this manner it is possible to obtain maximum benefits for citizen as well as the best use of resources for the health systems of different countries. Within these processes and approaches to treatment, the health care assistance model has to be planned not only to lead to the diagnosis and treatment of an acute ischemic stroke event, but also the decision-making center of a differential diagnosis that must urgently involve other specialties and competences.

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Tables

Table 1 Articles included in the review

TITLE	YEAR	AUTHORS (The first two)	JOURNAL/EDITOR/SPONSOR
Outcome, use of resources and their relationship in the treatment of AMI, stroke and hip fracture at European hospitals.	2015	Häkkinen, U., Rosenqvist, G., et al.	<i>Health economics</i>
Cost-effectiveness analysis of new oral anticoagulants to prevent stroke in patients with non-valvular atrial fibrillation in Italy	2014	Ravasio R., Pedone M.P., et al.	<i>PharmacoEconomics Italian Research Articles</i>
Economic impact of Stroke Unit in the Campania region	2014	Scaletti, A., Lauro E., et al.	<i>Ig. Public Health</i>
Robotic Upper Limb Rehabilitation after Acute Stroke by NeReBot: Evaluation of Treatment Costs.	2014	Masiero, S., Poli, P., et al.	<i>BioMed research international</i>
Rivaroxaban economic assessment	2013	Capri S., Veneziano M.A.	<i>Notebooks of the Italian Journal of Public Health</i>
A standardized vascular disease health check in europe: a cost-effectiveness analysis.	2013	Schuetz, C. A., Alperin, P., et al.	<i>PloS one</i>
Evaluation of different strategies for identifying asymptomatic left ventricular dysfunction and pre-clinical (stage B) heart failure in the elderly. Results from 'PREDICTOR', a population based-study in central Italy.	2013	Mureddu, G. F., Tarantini, L., et al..	<i>European journal of heart failure</i>
Incidence and costs of hip fractures vs strokes and acute myocardial infarction in Italy: comparative analysis based on national hospitalization records.	2012	Piscitelli, P., Iolascon, G., et al.	<i>Clinical interventions in aging</i>
The social and economic burden of stroke survivors in Italy: a prospective, incidence-based, multi-centre cost of illness study.	2012	Fattore, G., Torbica, A., et al.	<i>BMC neurology</i>
The cost of first-ever stroke in Valle d'Aosta, Italy: linking clinical registries and administrative data.	2012	Bottacchi, E., Corso, G., et al.	<i>BMC health services research</i>
Economic assessment of treatment with alteplase for Ischemic stroke patients in the	2010	Lucioni, D. C., Mazzi, S., et al.	<i>PharmacoEconomics Italian Research Articles</i>

acute stage, with reference to Italy			
Cost-Effectiveness of Prasugrel Versus Clopidogrel in Patients With Acute Coronary Syndromes and Planned Percutaneous Coronary Intervention Results From the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction TRITON-TIMI	2010	Mahoney, E. M., Wang, K., et al.	<i>Circulation</i>
Socioeconomic differences in stroke incidence and prognosis under a universal healthcare system.	2009	Cesaroni, G., Agabiti, N., et al.	<i>Stroke</i>
Physicians' views on resource availability and equity in four European health care systems.	2007	Hurst, S. A., Forde, R., et al.	<i>BMC Health Services Research</i>
The impact of different rehabilitation strategies after major events in the elderly: the case of stroke and hip fracture in the Tuscany region.	2007	Carinci, F., Roti, L., et al.	<i>BMC health services research</i>

Source: Our Processing

Table 2 Content analysis of articles included in the review

References	Study design	Population	Type of analysis	Main results
Masiero, S., Poli, P., Armani, M., Ferlini, G., Rizzello, R., & Rosati, G. (2014).	Randomized controlled clinical trial (RCT). The two randomized controlled trials tested two different robotic protocols in comparison to standard rehabilitation treatment. Both protocols lasted 5 weeks and included two daily sessions of robotic treatment for five days a week.	NeReBot was tested in two different clinical trials. Both studies involved hemiparetic subjects in the acute and subacute phases of their stroke, enrolled within 15 days after stroke.	Evaluation of Treatment Costs. To evaluate the costs of robotic and control treatment in the acute and subacute phases post stroke.	Based on a cost of about C33,000 gross per year, we get an hourly cost of therapist close to C19. Considering 30-minute robotic treatment sessions (to be repeated twice a day), according to the four different levels of supervision (from 1:1 to 1:4, i.e., 30, 15, 10, and 7.5 minutes per session). An hourly treatment cost of robotic therapy ranging between C25 (first week) and C11 (last weeks), according to the different impact of the cost of the operator with respect to the hourly cost of the equipment
Cesaroni, G., Agabiti, N., Forastiere, F., & Perucci, C. A. (2007).	This study is based on information from the Health Information System of the Lazio region. It used a small-area SEP index. Were calculated age-adjusted incidence rates and rate ratios by SEP for fatal and nonfatal stroke subtypes	Were selected all hospitalizations and deaths with a diagnosis, or cause of death, of ischemic or hemorrhagic stroke that occurred from 2001 to 2004 in 35- to 84-year-old Rome residents.	Socioeconomic evaluation. The authors used Poisson models to calculate age-adjusted incidence rates in the 35- to 84-year-old Rome population by stroke subtype.	Total of 10,033 incident strokes (75% ischemic) were observed. Incidence rates (per 100 000) for ischemic and hemorrhagic stroke were: 104 and 34 in men and 81 and 28 in women, respectively. There were socioeconomic

	<p>using Poisson regression. Logistic regression was used to study outcomes by SEP (30-day mortality, and among 1-month survivors: 1-year mortality, hospital readmissions for a successive stroke, and cardiovascular diseases).</p>			<p>disparities in stroke incidence in both genders (rate ratios between extreme SEP categories in ischemic and hemorrhagic stroke: 1.76; 95% CI, 1.59 to 1.95; 1.50; 95% CI, 1.26 to 1.80 in men; 1.72; 95% CI, 1.55 to 1.91; 1.37; 95% CI, 1.15 to 1.63 in women).</p>
<p>Mahoney, E. M., Wang, K., Arnold, S. V., Proskorovsky, I., Wiviott, S., Antman, E., et al. (2010).</p>	<p>The economic analysis was prespecified and performed using data from all patients enrolled in 8 prespecified countries. The primary economic end point was total in-trial costs; if one drug proved to be both more effective and more costly than the other, an evaluation of incremental cost-effectiveness would be performed.</p>	<p>Detailed resource use data were prospectively collected for all patients recruited from 8 countries (United States, Australia, Canada, Germany, Italy, Spain, United Kingdom, and France; n_3373 prasugrel, n_3332 clopidogrel)</p>	<p>Cost-effectiveness. Cost-effectiveness was evaluated from the perspective of the US healthcare system by using a lifetime horizon; the primary end point was the incremental cost per life year gained. The incremental cost effectiveness ratio (ICER) for prasugrel versus clopidogrel was calculated by dividing the net cost associated with prasugrel treatment by the difference in lost life expectancy resulting from death, nonfatal MI, or nonfatal stroke</p>	<p>Prasugrel was associated with life expectancy gains of 0.102 years (95% confidence interval, 0.030 to 0.180), primarily because of the decreased rate of nonfatal MI. Thus, compared with clopidogrel, prasugrel was an economically dominant treatment strategy. If a hypothetical generic cost for clopidogrel of \$1/d is used, the incremental net cost with prasugrel was \$996 per patient, yielding an incremental cost-effectiveness ratio of \$9,727 per life-year gained.</p>

<p>Hurst, S. A., Forde, R., Reiter-Theil, S., Slowther, A. M., Perrier, A., Pegoraro, R., & Danis, M. (2007).</p>	<p>A cross-sectional survey to ascertain generalist physicians' perspectives on resources allocation and its consequences in Norway, Switzerland, Italy and the UK.</p>	<p>A random sample of 400 individuals was drawn in each country in proportions of general practitioners and general internists reflecting that of each national physician population.</p>	<p>Socioeconomic evaluation. They analyze the evaluations of doctors in relation to the allocation of resources and related organizational models of health systems.</p>	<p>Survey respondents (N = 656, response rate 43%) ranged in age from 28–82, and averaged 25 years in practice. Most respondents (87.7%) perceived some resources as scarce, with the most restrictive being. Most respondents (78.7%) also reported some patient groups as more likely than others to be denied beneficial care on the basis of cost. Almost all respondents (97.3%) found at least one cost-containment policy acceptable. The types of policies preferred suggest that respondents are willing to participate in cost-containment, and do not want to be guided by administrative rules (11.2%) or restrictions on hospital beds (10.7%).</p>
<p>Carinci, F., Roti, L., Francesconi, P., Gini, R., Tediosi, F., Di Iorio, T., et al. (2007).</p>	<p>The aims were to describe rehabilitation patterns for elderly patients with stroke and hip fracture and to investigate mortality risk during the 6 month post</p>	<p>The study population refers to residents in Tuscany aged at least 65, discharged from acute hospital wards between 1/7/2001 and 30/6/2003 with a primary</p>	<p>Efficacy or effectiveness evaluation. Univariate statistics and graphical outputs were used to describe rehabilitation services provided after the</p>	<p>Out of the 13,354 subjects with stroke identified in the reference time interval, 16.7% died during the index admission and further 13.8% within 180 days after</p>

	acute period.	diagnosis of Stroke never admitted for stroke during the previous three years, or with a primary diagnosis of hip fracture not admitted with the same diagnosis during the previous 28 days.	index event. Percentages are expressed in relation to either the total population experiencing the index event (including in-hospital deaths), or, when appropriate, to the subjects discharged alive. Proportional hazards regression was the basis of multivariate survival analysis. Multivariate Cox regression analysis was used to evaluate the independent association between rehabilitation and increased mortality, adjusting for all other individual characteristics.	discharge. Average LOS was longer among subjects with hip fractures, albeit less variable. In terms of acute care, 549 patients with stroke (4.1%) were admitted to stroke units while 2,801 patients with hip fracture (22.6%) underwent surgery within 2 days from admission.
Capri, S., Veneziano, M.A. (2013).	This study illustrates the results of the analysis concerning cost-effectiveness and budget impact of Rivaroxaban in the treatment of the FANV, and related health and economic consequences at the occurrence of stroke events.	The population included in the base case is constituted by patients with FANV (adults 73 years old) and at moderate / high risk of stroke.	Cost-effectiveness. The cost-effectiveness analysis assumes as samples 73 years old adult subjects in a period of time of 30 years conducted under a NHS perspective.	The introduction of Rivaroxaban in the national and regional market would result in a reduction of the total costs borne by the SSN (€ 32,585,432 in the third year) as well as the number of strokes (2,504 events avoided in the third year).

<p>Ravasio, R., Pedone, M. P., & Ratti, M. (2014).</p>	<p>A Markov decision model with a 3-month cycles and a lifetime horizon were adopted. Efficacy and quality of life were estimated from clinical trials and published literature.</p>	<p>Italian Population (Istat Data of 2013).</p>	<p>Cost-effectiveness. The cost-effectiveness analysis was performed from the perspective of the Italian National Health Service</p>	<p>The incremental cost-effectiveness ratio (ICER) of dabigatran was €6,800/QALY versus warfarin and €5,787/QALY versus apixaban.</p>
<p>Häkkinen, U., Rosenqvist, G., Iversen, T., Rehnberg, C., & Seppälä, T. T. (2015).</p>	<p>The comparison of quality (survival), use of resources and their relationship in the treatment of three major conditions (acute myocardial infarction (AMI), stroke and hip fracture), in hospitals in five European countries (Finland, Hungary, Italy, Norway and Sweden).</p>	<p>Total number of patients 17,735 Number of patients in sample 14,571 Number of hospitals 35 Number of hospitals with stroke unit 10</p>	<p>Cost-Quality. In this study was compared the quality and cost of care for AMI, stroke and hip fracture patients in about 250 European hospitals in five countries.</p>	<p>The number of hospitals performing statistically significantly better than average was 8 in Finland (30% of all hospitals), 5 in Hungary (6%), 18 in Italy (52%), and 18 in Sweden (28%).</p>
<p>Schuetz, C. A., Alperin, P., Guda, S., van Herick, A., Cariou, B., Eddy, D., et al. (2013).</p>	<p>They simulated a clinical trial comparing seven health check strategies to current levels of care in seven countries.</p>	<p>Were used country-specific data from Denmark, France, Germany, Italy, Poland, and the United Kingdom to generate simulated populations of individuals aged 40–75 eligible for health checks in those countries. In Italy are 25,000 people; Middle Age 54,6</p>	<p>Cost Effectiveness. Was used the Archimedes Model to estimate the cost effectiveness of offering a range of health check strategies to individuals in six European populations, compared to current levels of care in each country.</p>	<p>Compared with current care, health checks reduced the incidence of MACE (6–17 events prevented per 1,000 people screened) and diabetes related microvascular complications (5–11 events prevented per 1,000 people screened), and increased QALYs (31–59 discounted QALYs) over 30 years, in all countries. The cost per QALY of offering a</p>

				<p>health check to all individuals in the study cohort ranged from J14903 (France) to cost saving (Poland). Pre screening the population and offering health checks only to higher risk individuals lowered the cost per QALY. Pre-screening on the basis of obesity had a cost per QALY of J10,200 (France) or less, and pre-screening with a non-invasive risk score was similar</p>
<p>Mureddu, G. F., Tarantini, L., Agabiti, N., Faggiano, P., Masson, S., Latini, R., et al. (2013).</p>	<p>All subjects underwent physical examination, biochemistry/NTproBNP assessment, 12-leadECG, and Doppler transthoracic echocardiography (TE). Five strategies were evaluated including ECG, NT-proBNP, TE, and their combinations.</p>	<p>A sample of 1,452 subjects aged 65–84 years were chosen from the original cohort of 2001 randomly selected residents of the Lazio Region (Italy), as a part of the PREDICTOR survey. Subjects older than 75 years, and with at least two additional risk factors were defined as being high-risk for HF(435), whereas the remaining 1017 were defined at low risk.</p>	<p>Cost Effectiveness. Screening characteristics and cost-effectiveness (cost per case) of the five strategies to predict systolic (EF,50%) or diastolic ALVD and pre-clinical HF(stageB) were compared.</p>	<p>Among the total 1,452 subjects included in the present post-hoc analysis, 435 were at high risk and 1,017 at lowrisk. The prevalence of systolic AVLD did not differ between high-risk and low-risk groups. It was able to identify 14 of 22 cases (63.6%) of systolic ALVD (EF ,50%), saving E3.076 per any case detected compared with strategy . This strategy showed less accuracy in detecting diastolic ALVD (only</p>

				13.9% including mild diastolic dysfunction), with many undiagnosed cases (86.1%). However, it identified 35.2% of subjects with moderate to severe diastolic AVLD and had the lowest cost for each case detected (E90).
Piscitelli, P., Iolascon, G., Argentiero, A., Chitano, G., Neglia, C., Marcucci, G., et al. (2012).	In this study they aimed to compare the incidence and costs of hip fragility fractures in Italian elderly people versus those of major cardiovascular diseases (strokes and acute myocardial infarctions [AMI]) occurring in the whole adult population. They analyzed hospitalization records maintained at the national level by the Italian Ministry of Health for the diagnosis of hip fractures (ICD-9-CM codes 820–821), AMI (code 410), hemorrhagic (codes 430, 431, 432) and ischemic strokes (codes 433–434), and TIA (code 435) between 2001–2005.	Italian population among those aged 45–100 years old: Hospital and rehabilitation costs following strokes in the Italian population among those aged 45–100 years old in five years (2001-2005).	Cost analysis. This study compares costs of hip fractures in the elderly with those generated by strokes and AMI in Italy. Cost analysis concerning strokes was based on DRG 14 (hemorrhagic and ischemic strokes) and DRG 15 (TIA).	The incidence of hip fractures in elderly people has increased (+12.9% between 2001 and 2005), as well as that of AMI (+20.2%) and strokes (hemorrhagic: +9.6%; ischemic: +14.7) occurring in the whole adult population. Rehabilitation costs following strokes reached about 3 billion Euros in 2005, but rehabilitative costs of hip fractures and AMI were comparable (about 530 million Euros in 2005).

<p>Fattore, G., Torbica, A., Susi, A., Giovanni, A., Benelli, G., Gozzo, M., &Toso, V. (2012).</p>	<p>This study estimates the one-year societal costs due to a stroke event in Italy and investigates variables associated with costs in different phases following hospital admission. The patients were enrolled in 44 hospitals across the country and data on socio-demographic, clinical variables and resource consumption were prospectively surveyed for 411 stroke survivors at admission, discharge and 3, 6 and 12 months post the event.</p>	<p>Total number of patients enrolled in the study(546 in Italy): North Italy 252, Centre Italy 101, South Italy 193.</p>	<p>Costs analysis. Adopted a micro-costing procedure to identify cost generating components and the attribution of appropriate unit costs for three cost categories: direct healthcare, direct non-healthcare and productivity losses. Multiple linear regression analyses were performed to determine predictors of costs incurred by stroke patients during the acute phase and follow-up of 1 year.</p>	<p>On average, one-year healthcare and societal costs amounted to €11,747 and € 19,953 per stroke survivor, respectively. The major cost component of societal costs was informal care accounting for € 6,656 (33.4% of total), followed by the initial hospitalisation, (€ 5,573; 27.9% of total), rehabilitation during follow up (€ 4,112; 20.6 %), readmissions (€ 439) and specialist and general practitioner visits (€ 326). Mean drug costs per patient over the follow-up period was about € 50 per month. Costs associated to the provision of paid and informal care followed different pattern and were persistent over time (ranging from € 639 to € 597 per month in the first and the second part of the year, respectively).</p>
<p>Bottacchi, E., Corso, G., Tosi, P., Morosini, M. V., De Filippis, G., Santoni, L., et al. (2012).</p>	<p>Was conducted a longitudinal, retrospective, bottom-up cost of illness study, to evaluate clinical</p>	<p>Patients affected by a first cerebrovascular event, including subjects with ischaemic, haemorrhagic or</p>	<p>Cost analysis. A clinical and economic outcomes estimation. They conducted a longitudinal,</p>	<p>The majority of patients (71.5%) were affected by ischaemic stroke. Overall, per patient costs were</p>

	<p>and economic outcomes of a cohort of patients affected by a first cerebrovascular event, including subjects with ischaemic, haemorrhagic or transient episodes. The analysis intended to detect direct costs, within 1, 2 and 3 years from the index event.</p>	<p>transient episodes: at first year, 800 (58.0%) of 1,380 patients included in the registry were included in the analysis. The analysis at 2 years included 549 patients. Subjects eligible for the analysis at 3 years were 268.</p>	<p>retrospective, bottom-up cost of illness study.</p>	<p>€7,079. Overall costs significantly differ according to the type of stroke, with costs for haemorrhagic stroke and ischaemic stroke amounting to €9,044 and €7,289. Hospital costs, including inpatient rehabilitation, were driver of expenditure, accounting for 89.5% of total costs. The multiple regression model showed that sex, level of physical disability and level of neurological deficit predict direct healthcare costs within 1 year. The analysis at 2 and 3 years (per patient costs: €7,901 and €8,874, respectively) showed that majority of costs are concentrated in the first months after the acute event.</p>
<p>Scaletti, A., Lauro, E., Belfiore, P., Zamparelli, B., Liguori, G., & SIHHS (2014).</p>	<p>This study project is based on two parallel work hypotheses. The first one quantifies the economic resources saved by comparing a scenario that sees the creation of a new SU and one without it. The second one, by contrast,</p>	<p>In the first case, the reference population is considered the one of the subjects affected by stroke in the year 2009 amounting to 14,737 individuals. In the second case, the population is the percentage of thrombolyses performed</p>	<p>Costs analysis. This study proposes a cost-analysis, in the perspective of the Italian National Health Service.</p>	<p>The analysis quantifies in € 5,810,894 the annual savings achievable thanks to the implementation of a stroke unit. While from the second case analyzed, it was possible to estimate final savings of € 43,798,147 arising from</p>

	weighs the feasible economies in case where all patients with eligibility criteria make use of thrombolytic therapy; in this case the compared scenarios are the ideal one (negotiable patients) versus the real one (treated patients)	in 2009 (59 subjects treated, equal to 0.4% of patients affected by stroke) then compared to (8%) of the subjects who reached DEA with the eligibility criteria for thrombolysis (1,179).		serious disabilities avoided, as the difference between the cases treated and the treatable ones.
Lucioni, D. C., Mazzi, S., Micieli, G., Sacchetti, M. L., & Toni, D. (2010).	A life-time Markov model compares alteplase added to standard care versus standard care alone. The endpoint of the study is the cost per QALY (Quality Adjusted Life Year) gained.	Italian Population (Istat Data of 2012)	Cost Effectiveness. This study proposes a cost-effectiveness analysis, in the perspective of the Italian National Health Service.	In the base case alteplase resulted a dominant strategy (costs saved per patient: €409). Both in the deterministic and probabilistic sensitivity analysis, alteplase dominance was confirmed in most cases.

Source:

Our

Processing

Diagram 1: Selection process of reviewed articles

