AMSR: 30-35 (2024)
Research Article
www.medical.researchfloor.org

The value of thrombolysis for the management of acute ischemic stroke: a cost effectiveness analysis based on real world data from the SUN4P study

Panos Stafylas[1¥*], Olga Siskou[2*], Petros Galanis[3], Olympia Konstantakopoulou[3], Iliana Karagkouni[3], Marianthi Karaiskou[1], Argyro Tountopoulou[4], Ioanna Kouzi[4], Sofia Vasilopoulou[4], Ioannis Kalliontzakis[5], Christos Savopoulos[6], Efstathios Manios[7], Evangelos Tsampalas[8], Haralampos Milionis[9], Athanasios Protogerou[10], Daphne Kaitelidou[3#], Eleni Korompoki[7,11#], George Ntaios[11,12#], Konstantinos Vemmos[11,13]

**Equal first, # Equal last*

[1]*HealThink (Medical Research & Innovation PC), Thessaloniki, Greece*
[2]*Center for Health Services Management and Evaluation, Department of Nursing National and Kapodistrian University of Athens, Athens, and University of Piraeus, Piraeus Greece*
[3]*Center for Health Services Management and Evaluation, Department of Nursing National and Kapodistrian University of Athens, Athens, Greece*
[4]*1st Department of Neurology, Eginition Hospital, National and Kapodistrian University of Athens, Athens, Greece.*
[5]*Department of Neurology, General Hospital of Chania, Creta, Greece.*
[6]*1st Medical Propedeutic Department of Internal Medicine, Aristotle University of Thessaloniki, AHEPA Hospital, Thessaloniki, Greece.*
[7]*Department of Clinical Therapeutics, Alexandra Hospital, National and Kapodistrian University of Athens, Athens, Greece*
[8]*Department of Neurology, Panarkadikon General Hospital, Tripoli, Greece.*
[9]*Department of Internal Medicine, School of Medicine, University of Ioannina, Ioannina, Greece*
[10]*Cardiovascular Prevention & Research Unit in Laiko General Hospital of Athens at the Medical School of the National & Kapodistrian University of Athens, Greece*
[11]*Hellenic Stroke Organization, Greece*
[12]*Department of Internal Medicine, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa, Greece*
[13]*Hellenic Cardiovascular Research Society, Athens, Greece*

ABSTRACT

Background: Previous studies have shown that patients with Acute Ischemic Stroke (AIS) treated with recombinant tissue plasminogen activator (rtPA) have better clinical and in several cases economic outcomes than those who are not. However, the cost-effectiveness of rtPA in the Greek setting is totally unknown. This study aims to evaluate the cost-effectiveness of rtPA for the management of AIS in Greece based on real world data (RWD).

Methods: A cost-effectiveness model was developed in Microsoft® Excel to examine the clinical and economic impact of rtPA from a Greek third-party payer perspective based on RWD collected during the "Improving Stroke Care in Greece in Terms of Management, Costs and Health Outcomes" project, with the participation of nine Greek hospitals from different cities. The primary outcome of the analysis was the incremental cost-effectiveness ratio (ICER) expressed in euros per quality adjusted life year (QALY). The primary clinical outcome was the mRS value at 3 months. Robustness of the results was tested using both one-way and probabilistic sensitivity analyses.

Results: Compared with conservative management, rtPA led to 0.009 incremental QALYs per patient in the first 3 months. The total cost per patient incurred by the rtPA group was 2,196.65€, compared to 2,499.45€ in the conservative treatment group, leading to 302.79€ savings per patient, indicating that rtPA is more effective and costs less than conservative management from a Greek third-party payer perspective. However, probabilistic sensitivity analyses (PSA) showed that there is a significant variability and the probability of rtPA to be cost effective or dominant in the Greek setting is between 58.9%-74.1% within the threshold of one to three times the national GDP per capita.

Conclusion: Intravenous rtPA represents a dominant or cost-effective strategy for the management of AIS in Greece. The analysis may have underestimated the potential benefits of rtPA. Although this study provides additional evidence to decision-makers, more data are required to improve the robustness of the conclusion.

Keywords. *Stroke, thrombolysis, recombinant tissue plasminogen activator, alteplase, cost-effectiveness, QALY*

Citation: Panos Stafylas, Olga Siskou, Petros Galanis, Olympia Konstantakopoulou, Iliana Karagkouni, Marianthi Karaiskou, Argyro Tountopoulou, Ioanna Kouzi, Sofia Vasilopoulou, Ioannis Kalliontzakis, Christos Savopoulos, Efstathios Manios, Evangelos Tsampalas, Haralampos Milionis, Athanasios Protogerou, Daphne Kaitelidou, Eleni Korompoki, George Ntaios, Konstantinos Vemmos (2024). The value of thrombolysis for the management of acute ischemic stroke: a cost effectiveness analysis based on real world data from the SUN4P study. *Journal of American Medical Science and Research.*

DOI: https://doi.org/10.51470/AMSR.2024.03.01.30

Received on: 19 January, 2024
Revised on: 08 March, 2024
Accepted on: 27 April, 2024

Corresponding Author: ***Panos Stafylas***
Email Address: ***panos@healthink.info***

INTRODUCTION

Stroke is one of the leading causes of morbidity, mortality and disability worldwide.[1],[2] The most recent Global Burden of Disease (GBD) indicated that in 2019 around the world, there were 12.2 million incident cases of stroke (one stroke every three seconds) and 101 million prevalent cases.1,2 Recently, OECD reported that he average mortality rate over one year for ischaemic stroke was 14%, but there was a significant deviation among the different countries with a range from 5% to 25%.[3]

Because of the high incidence and the subsequent disability, stroke constitutes a significant clinical, economic and social burden for the societies. In 2019, it was estimated that 143 million disability-adjusted life-years (DALYs) due to stroke2, and the total estimated cost of stroke in 2017 was US$861 billion, about 1.2% of the global GDP.1 Although, the last 30 years the age-standardised rates of stroke incidence decreased, the absolute number of incident strokes presented an increasing trend of 70%, while the stroke-related DALYs increased by 32%. In accordance with the World Stroke Organisation Global Stroke Fact Sheet 2022, approximately 25% of individuals will experience a stroke in their lifetime, most of them an ischemic one.[1]

Since all projections show that the burden of stroke in Europe will continue to increase4, it is urgent to identify and apply the most-effective methods for the primary prevention and management of stroke in each specific setting. Intravenous recombinant tissue plasminogen activator (rtPA) is an effective treatment for Acute Ischemic Stroke (AIS) if administered within 4.5 hours of symptoms onset.5-7 In patients with AIS, rtPA administration within 4.5 hours of symptom onset, compared with placebo, significantly improved clinical outcome at 90 days after stroke onset, as assessed by the percentage of patients with modified Ranking scale (mRs) scores of 0 or 1.5,7 Last years, several cost-effectiveness analyses showed that IV rtPA was a dominant or cost-effective strategy for the patients with AIS compared with conservative management without rtPA.8-12 Despite of the above evidence, thrombolysis rates are still significantly low, with significant variations among EU countries but also among different regions in each country.[13]

Greece is one of the countries with a very low rate of thrombolysed ischemic stroke patients. [13] It is estimated that approximately 30,000–35,000 new strokes occur anually, and represent one of the two most prevalent causes of death, accounting for more than 10% of all deaths.[14]-[16] The total annual expenditure associated with strokes in Greece has been estimated at approximately 650 million Euros.[17] In a recent study for the economic burden of stroke in Greece related with atrial fibrillation,[15] it was estimated that the total cost per patient was 6,273 euros in 2018, regardless of the health state, i.e regardless of whether individual has previously experienced a stroke episode or is a new incident patient. The key cost drivers included productivity losses of informal caregivers (21.1%), productivity losses of patients (19.7%), hospitalizations (15.0%) and rehabilitation (14.1%), accounting for about 70% of the total cost.[15]

There are inadequate data on cost-effectiveness of rtPA in Greece. Because of differences in healthcare systems, costs and reimbursement methods, non-Greek data may not be relevant with the Greek setting and decision-makers hesitate to invest more resources on stroke units and thrombolysis of acute ischemic stroke.

The objective of this study is to assess the cost-effectiveness of rtPA for the management of AIS using real world data (RWD) from the Greek setting, and to provide the required evidence to the decision-makers.

METHODS

Study population

The study population derived retrospectively from the "Improving Stroke Care in Greece in Terms of Management, Costs and Health Outcomes - SUN4Patients" project. The SUN4P study is a prospective cohort multicenter study of patients with first ever acute stroke, hemorrhagic and ischemic, (ICD-10 codes: I61, I63 and I64) admitted within 48 hours of symptoms onset to nine National Health System and University hospitals. The study protocol has been registered in ClinicalTrials.gov (NCT04109612). Detailed data were prospectively recorded for each patient, including demographics, medical history and associated cardiovascular risk factors, stroke onset, length of hospital stay, stroke characteristics, clinical findings and vital signs on admission, laboratory investigations, and administered treatment. Body weight and height were measured by the stroke nurse on admission. The presented study methodology and analysis utilised data derived from SUN4Patients project and followed the logical framework of other relevant analyses that have been already conducted based on this project's scope.[18],[19] However, for the needs of this analysis, all eligible patients were followed-up for 3 months. Data analysis included clinical outcomes and healthcare resources use. The study sample consisted of the 27 patients who have received thrombolysis with IV rtPA and 27 pairwise matched controls stratified by age, sex and severity on admission (NIHSS score), eligible for thrombolysis who have not been thrombolysed and blinded to 3 months patient's outcomes. The primary clinical outcome of the analysis was the modified Rankin Scale (mRS, 0-6) at 3 months.[20] A logistic regression analysis was performed to analyse the association between the mRS score at 3 months from admission after controlling for age, gender and NIHSS score at admission.

Cost-Effectiveness Analysis

A decision analytic model was used to compare health and economic outcomes of rtPA vs no-rtPA for the management of AIS (Figure 1). Possible states included: no symptoms (R0), no significant disability (R1), minimal disability (R2), moderate disability (R3), moderate to severe disability (R4), severe disability (R5) and death (R6). Utility values stratified by mRS category were derived from the literature (Table 1).[21] Quality-adjusted life years (QALYs) were measured by multiplying years of life (days of life in the first three months) by the above utility scores.

The analysis was performed from a third-party payer perspective (EOPYY). EOPYY is the National Organization for Health Care Services Provision in Greece, covering more than 95% of the Greek population. This organisation provided the actual cost paid (by EOPYY) for the management of AIS and its consequences for all study participants, included initial and possible subsequent hospitalisations, medications, blood tests and imaging, outpatient management and rehabilitation. The time horizon of the model was 3 months, which was considered clinically appropriate. Discounting was not applicable due to the short duration of the analysis. The primary outcome of the economic evaluation was the incremental cost-effectiveness ratio (ICER) expressed in euros per QALY.

Uncertainty analyses

One-way sensitivity analyses (OWSA) as well as probabilistic sensitivity analyses (PSA) were performed to validate the robustness of the cost-effectiveness results. OWSA were conducted by varying variables by +10/-10 % of their original (baseline) values to estimate their effect to the baseline ICER calculations. PSA was conducted by simulating the health and economic outcomes of 1,000 pairs of hypothetical individuals to assess the variability (robustness) of ICER. In each simulation all parameters varied randomly from the predefined distribution for each parameter.

RESULTS

Despite the non-randomized design of the study, there were no significant differences in the demographic and clinical characteristics of the two groups (rtPA vs no-rtPA) (Table 2). Most of the eligible patients were older than 70 years old (with an age range from 36 to 95 years old), less than 50% of them female, 74% hypertensives, 17% diabetics, 30% with atrial fibrillation (one in four from patients with AF, newly diagnosed). The analysis showed that rtPA is more effective than conservative treatment (non-rtPA) for the management of patients with AIS based on RWD from the Greek setting, gaining 0.009 incremental QALYs in the 3 months' time horizon. This benefit has been gained with parallel savings of 302.79€ per patient. The average total cost paid by the social security system for the patients receiving rtPA in the first three months after admission was 2,196.65€ vs 2,499.45€ for the patients not receiving rtPA. The results indicate that rtPA is a dominant strategy for the management of AIS from a Greek third-party payer perspective because it is more effective and costs less than conservative treatment (Table 3).

OWSA confirmed the robustness of the conclusion and showed that index hospitalisation cost was the most important factor for the analysis. However, PSA showed that there is a significant variability in simulated ICER and that the probability of rtPA to be cost effective or dominant in the Greek setting is between 58.9%-74.1% within the threshold of one to three times the national GDP per capita (15,424€ is the last available Greek GDP per capita for 2020, reported by the Hellenic Statistical Authority). This variability is presented in the cost-effectiveness plane (Figure 2) and the cost-effectiveness acceptability curve (Figure 3).

DISCUSSION

Our analysis indicates that intravenous rtPA administered for the management of AIS in the Greek setting in less than 4.5 hours after symptoms onset is associated with better clinical outcomes and a lower cost for the national payer (EOPYY) indicating that it is a potentially dominant or cost-effective treatment strategy. The analysis was conducted based on RWD collected prospectively in seven public and university hospitals in different Greek cities as part of the SUN4P project. Moreover, healthcare resources use, and total treatment cost were provided directly from the national payor, for each individual patient participating in the study, in accordance with study protocol as approved by Ethics Committee. To the best of our knowledge, this study represents one among few studies that proceeded to the economic evaluation of stroke management in Greece based on RWD, prospectively collected. In addition, this study also stands as one the first economic evaluations for the Greek setting which has considered the actual burden for the national payor, with data provided directly by EOPYY.

Our findings are aligned with the international literature,[10,22,23] which clearly indicates that rtPA is a cost-saving or cost-effective treatment option compared with traditional treatment for patients with acute ischemic stroke.[24] The broad range of the reported ICERs, from dominant to >70,000$/QALY in different studies can be explained by the fact that available evidence lacks generalizability because of limited data and various assumptions, including utilities used in the models.[24]

Our study has also presented some limitations which have to be taken into account for the interpretation of the results. The study participants were only 54 (27 thrombolysed), which further indicates the urgency for action – it is obvious that in a total population of more than 750 ischemic strokes in the SUN4P project, someone would expect that more patients would be eligible and receive thrombolysis. However, we must mention that our study was conducted almost in parallel with the COVID-19 pandemic and that could be considered as a potential barrier for the administration of thrombolysis (e.g due to delays).

Another issue is the short duration of the follow-up but the results of our study can be confirmed by other relevant studies according to which most studies conducted for a year or less have a similar marginal difference in both costs and benefits between rtPA and no-rtPA arm.[24] Moreover, although this was considered clinically relevant, for administrative issues more feasible and aligned with international literature, it is expected that a longer follow-up could demonstrate additional benefits in terms of QALYs because of the lower disability of the patients thrombolysed early.

Overall, patients that received thrombolysis had a better mRS score at 3 months. It was not found difference in mortality rates within the 3 months' time horizon, however it is well established that worse mRS scores are associated with an excess risk of death in the long-term.[25] This means that clinical effect of rtPA might be even more evident in the long-term, which can lead to a subsequent further improvement to its economic value. This hypothesis has been confirmed by previous studies in Europe, USA, and China.[22-24]

Our analysis has partially considered rehabilitation costs. EOPYY has provided data for inpatient rehabilitation cost for 12 patients and for 8 out of 54 patients for outpatient rehabilitation, possibly because most of the other patients cover rehabilitation privately, due to administrative barriers in the reimbursement of stroke rehabilitation in Greece. A recent study by *Vemmos et al.* showed that 39% of direct healthcare costs for stroke in Greece were covered by the patients as out-of-pocket expenses and this percentage was even higher for rehabilitation.[15]

The perspective of the analysis was that of the national payor (EOPYY) and consequently indirect costs were not considered, although a recent study showed that indirect cost is a major driver of the total economic burden of stroke patients in Greece accounting for about 41% of the total cost.[17]

The main strength of our study is the use of RWD from the everyday clinical practice to estimate the cost-effectiveness of rtPA in Greece. As far as we are aware, this is the first economic evaluation for the use of rtPA in patients with AIS in the Greek healthcare setting. Given the fact that, the accessibility in rtPA is as low as 6.9% [26] of AIS patients in Greece, the results of the present study can be utilised to support decision-making and improve AIS management and patient's accessibility to more advanced treatment.

In any case, these findings must be interpreted with caution, considering that it is very likely that the study may have underestimated the potential benefits for rtPA and consequently may have contributed to the increased variability of the ICER, as presented in the acceptability curve.

CONCLUSION

In conclusion, intravenous rtPA represents a dominant or cost-effective strategy for the management of acute ischemic stroke in Greece, however with a significant variation in the PSA. Although this study provides additional evidence to decision-makers and the fact that may have underestimated the potential benefits of rtPA, more data are required to improve the robustness of the conclusions. The systematic collection of RWD for stroke management at national level could support decision-making at clinical and administrative level, to use available resources with the most efficient way.

Funding

SUN4P project has received funding from the Hellenic Foundation for Research and Innovation (HFRI) and the General Secretariat for Research and Technology (GSRT), under grant agreement Nb538.

Conflict of interest

Authors report no relationships that could be construed as a conflict of interest.

Acknowledgments

We thank Ms Alexopoulou H, Dr Dimas G., Ms Evaggelou H., Ms Fragkoulaki A., Ms Gamvroula A., Ms Garefou D., Ms Lypiridou M., Dr. Nick Kakaletsis, Ms Karagkiozi E., Ms Karapiperi A., Ms Kouridaki A., Mr Mavraganis G., Dr Myrou A., Ms Samara S., Mr Siopis G., Ms Vemmou A., for their efforts to collect clinical and follow up data of the under-study population. We also thank EOPYY for the provision of the economic data as well as Mr Christos Priftis for the interpretation of the data provided by EOPYY

Table 1. Mean Utility Values per modified Rankin Scale (mRS) Category

mRS Category	Utility
0	0,88
1	0,74
2	0,51
3	0,23
4	-0,16
5	-0,48
6	0,00

Abbreviations: mRS: Modified Rankin Scale; Data source: Ni et.al 2020 [21]

Table 2 . Demographic and clinical characteristics of study participants

Variables	rtPA (n=27)	no-rtPA (n=27)
Age [Mean (SD/Median)]	70.6 (11.7/72)	72 (13.6/76)
Female (n, %)	10 (37%)	12 (44.4%)
BMI [Mean (SD/Median)]	28.1 (5 / 27.8)	27.33 (4.85/27.53)
NIHSS score baseline [Mean (SD/Median)]	10.6 (5.16/10)	9.6 (4.2/9)
mRS 0-1 prior admission (n, %)	27 (100%)	22 (81.5%)
Smoking status (n, %)		
Never	*15 (55,6%)*	*15 (55,6%)*
Current or ex-smoker (<2years)	*9 (33,3%)*	*7 (25,9%)*
Ex-smoker (>2 years)	*3 (11,1%)*	*5 (18,5%)*
Hypertension %	20 (74%)	20 (74%)
Diabetes %	5 (18,5%)	4 (14.8%)
Coronary artery disease %	7 (25,9%)	2 (7,4%)
Atrial Fibrilation %	7 (25,9%)	5 (18.5%)
Dyslipidaemia %	9 (33,3%)	12 (44.4%)
Length of hospital stay [Mean (SD, Median)]	9.48 (6.8/7)	10 (9/7)

Abbreviations: rtPA – indicates recombinant tissue-type plasminogen activator; SD – standard deviation; mRS – modified Rankin Scale; NIHSS - National Institute of Health Stroke Scale; BMI – Body Mass Index.

Table 2 . Cost-Effectiveness analysis results

Parameter	rtPA	No-rtPA	Incremental
Cost	2.196,65 €	2.499,45 €	-302,79 €
QALYs	0,1605	0,1515	0,0090
ICER (€/QALY)			**Dominant**

Abbreviations: rtPA – recombinant tissue-type plasminogen activator; QALYs – Quality-adjusted life years; ICER – Incremental Cost-Effectiveness ratio.

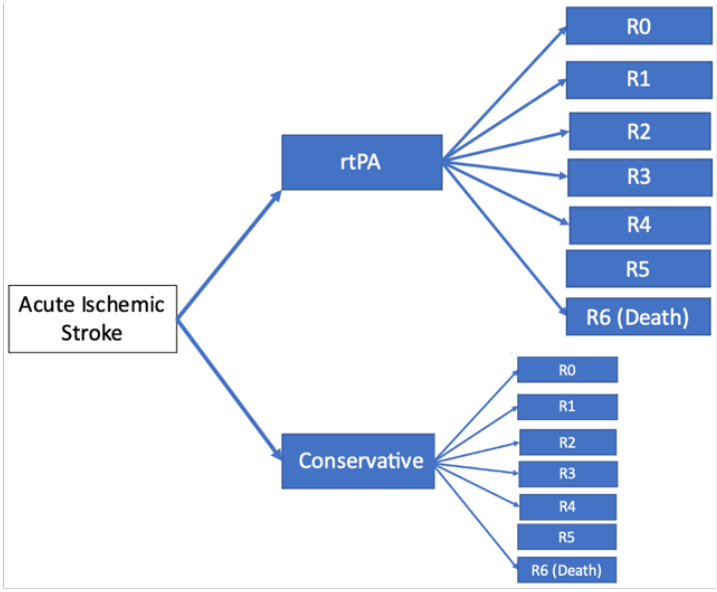

Figure 1. *Decision analytic model for intravenous thrombolysis with recombinant tissue-type plasminogen activator (rtPA) for the management of acute ischemic stroke within 4.5 hours from symptoms' onset.*

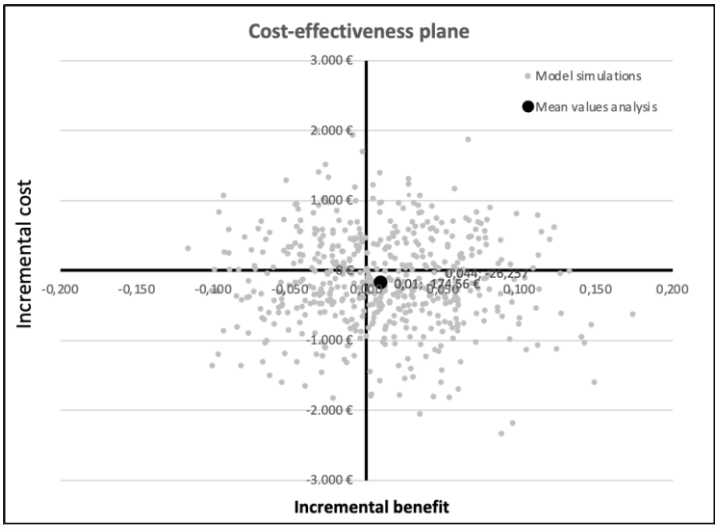

Figure 2. *Cost-effectiveness plane: each point represents a simulation. The dark square represents the mean values indicating that rtPA is more effective and costs less than the management of acute ischemic stroke without rtPA.*

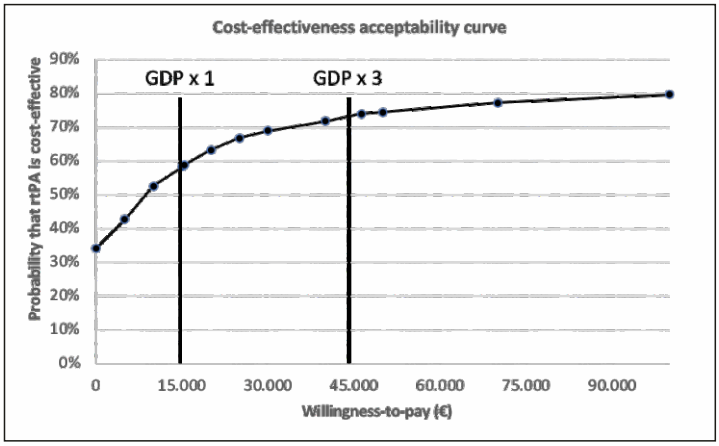

Figure 3. *Cost-effectiveness acceptability curve: The curve presents the probability that rtPA treatment to be cost-effective against different willingness-to-pay thresholds. The vertical lines represent a willingness-to-pay threshold of 15,424 € per QALY (one time the last published GDP per capita for Greece – GDP x 1) and of 46,272 € per QALY (three times the last published GDP per capita for Greece – GDP x 3).*

REFERENCES

1. Feigin VL, Brainin M, Norrving B, et al. World Stroke Organization (WSO): Global Stroke Fact Sheet 2022. International journal of stroke : official journal of the International Stroke Society. 2022;17(1):18-29.
2. Feigin VL, Stark BA, Johnson CO, et al. Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet Neurology. 2021;20(10):795-820.
3. Barrenho E, Haywood P, Kendir C, Klazinga NS. International comparisons of the quality and outcomes of integrated care: Findings of the OECD pilot on stroke and chronic heart failure. 2022.
4. Wafa Hatem A, Wolfe Charles D, Emmett Eva RGA, Johnson Catherine O. Wang Yanzhong (2020) Burden of Stroke in Europe. Stroke.51:2418-2427.
5. Emberson J, Lees KR, Lyden P, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. The Lancet. 2014;384(9958):1929-1935.
6. National Institute of Neurological D, Stroke rt PASSG. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995;333(24):1581-1587.
7. Berge E, Whiteley W, Audebert H, et al. European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. European stroke journal. 2021;6(1):I-LXII.
8. Boudreau DM, Guzauskas GF, Chen E, et al. Cost-effectiveness of recombinant tissue-type plasminogen activator within 3 hours of acute ischemic stroke: current evidence. Stroke. 2014;45(10):3032-3039.
9. Ehlers L, Müskens WM, Jensen LG, Kjølby M, Andersen G. National use of thrombolysis with alteplase for acute ischaemic stroke via telemedicine in Denmark: a model of budgetary impact and cost effectiveness. CNS Drugs. 2008;22(1):73-81.
10. Joo H, Wang G, George MG. Age-specific Cost Effectiveness of Using Intravenous Recombinant Tissue Plasminogen Activator for Treating Acute Ischemic Stroke. Am J Prev Med. 2017;53(6s2):S205-s212.
11. Sandercock P, Berge E, Dennis M, et al. Cost-effectiveness of thrombolysis with recombinant tissue plasminogen activator for acute ischemic stroke assessed by a model based on UK NHS costs. Stroke. 2004;35(6):1490-1497.
12. Tan Tanny SP, Busija L, Liew D, Teo S, Davis SM, Yan B. Cost-effectiveness of thrombolysis within 4.5 hours of acute ischemic stroke: experience from Australian stroke center. Stroke. 2013;44(8):2269-2274.
13. Aguiar de Sousa D, von Martial R, Abilleira S, et al. Access to and delivery of acute ischaemic stroke treatments: a survey of national scientific societies and stroke experts in 44 European countries. European stroke journal. 2019;4(1):13-28.

14. OECD, European Observatory on Health Systems Policies. Greece: Country Health Profile 2019, State of Health in the EU, OECD Publishing, Paris [cited 2020 Apr 12].. 2019.

15. Vemmos K, Boubouchairopoulou N, Stafylas P, et al. Estimation of the economic burden of atrial fibrillation-related stroke in Greece. Expert Review of Pharmacoeconomics & Outcomes Research. 2022;22(3):429-435.

16. Ministry of Health. Scientific Group for Cardiovascular Diseases, Therapeutic Protocol for anticoagulation treatment in atrial fibrillation patients; [cited 2020 Apr 12]. Available from: https://www.moh.gov.gr/articles/health/domes-kai-draseis-gia-thn-ygeia/kwdikopoihseis/therapeytika-prwtokolla-syntagografhshs/diagnwstika-kai-therapeytika-prwtokolla-syntagografhshs/5417-diagnwstika-kai-therapeytika-prwtokolla-syntagografhshskardiaggeiakwn-noshmatwn. 2018.

17. Wilkins E, Wilson, L., Wickramasinghe, K., Bhatnagar, P., Leal, J., Luengo-Fernandez, R., Burns, R., Rayner, M., & Townsend, N., . European cardiovascular disease statistics 2017. 2017.

18. Korompoki E, Ntaios G, Tountopoulou A, et al. Quality indicators and clinical outcomes of acute stroke: Results from a prospective multicenter registry in Greece (SUN4P). Journal of Clinical Medicine. 2024;13(3):917.

19. Siskou O, Galanis P, Konstantakopoulou O, et al. The Cost and the Value of Stroke Care in Greece: Results from the SUN4P Study. Paper presented at: Healthcare2023.

20. Broderick JP, Adeoye O, Elm J. Evolution of the Modified Rankin Scale and Its Use in Future Stroke Trials. Stroke. 2017;48(7):2007-2012.

21. Ni W, Kunz WG, Goyal M, Ng YL, Tan K, De Silva DA. Lifetime quality of life and cost consequences of delays in endovascular treatment for acute ischaemic stroke: a cost-effectiveness analysis from a Singapore healthcare perspective. BMJ Open. 2020;10(9):e036517.

22. Pan Y, Chen Q, Zhao X, et al. Cost-Effectiveness of Thrombolysis within 4.5 Hours of Acute Ischemic Stroke in China. PLOS ONE. 2014;9(10):e110525.

23. Ehlers L, Andersen G, Clausen LB, Bech M, Kjølby M. Cost-effectiveness of intravenous thrombolysis with alteplase within a 3-hour window after acute ischemic stroke. Stroke. 2007;38(1):85-89.

24. Kazley AS, Simpson KN, Simpson A, Jauch E, Adams RJ. Optimizing the Economic Impact of rtPA Use in a Stroke Belt State: The Case of South Carolina. Am Health Drug Benefits. 2013;6(4):155-163.

25. Huybrechts KF, Caro JJ, Xenakis JJ, Vemmos KN. The prognostic value of the modified Rankin Scale score for long-term survival after first-ever stroke. Results from the Athens Stroke Registry. Cerebrovasc Dis. 2008;26(4):381-387.

26. Siskou O, Korompoki E, Ntaios G, et al. Access of Stroke Patients' to Optimal Healthcare Technology in Greece: Messages to Policy Makers. Stud Health Technol Inform. 2020;272:421-424.

