ORIGINAL ARTICLE

ORAL ANTICOAGULANT TREATMENT WITH ANTIVITAMIN K IN ROMANIA. A COST-EFFECTIVENESS ANALYSIS OF USING INR HOME TESTING DEVICES

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Abstract

In Romania K antivitamin treatment is still monitored using INR (international normalized ratio) determination in the laboratory. Meanwhile there are available specialized devices that allow INR to be determined at home and thus self-monitoring of the treatment. A Markov model was used to determine the cost-effectiveness of using INR self-monitoring *versus* monitoring through classical methods. We carried out a budget impact analysis in the case of 1.5% of patients who would benefit from self-monitoring of INR paid by National Health Insurance House. Probabilistic outcomes resulting from setting the acceptability threshold to €30000/QALY, running a cohort with an average age of 65 for a period of 5 cycles (5 years) has led in 75% of cases to an incremental cost-effectiveness ratio (ICER) below the acceptability threshold. The Budget Impact Analysis showed that shifting 1.5% of the current cases on self-determination of INR will require a supplementary expense in the first year of €813640. Starting with the 5th year, the health insurance system will obtain progressive savings of €252419. The study findings showed that in Romania, self-monitoring of INR could be regarded as a cost-effective and sustainable intervention for the patients receiving oral anticoagulant therapy.

Rezumat

În România tratamentul cu antivitamine K este încă monitorizat utilizând determinarea INR (international normalized ratio) în laborator. În același timp, sunt disponibile dispozitive specializate care permit determinarea INR la domiciliu și, prin urmare, auto-monitorizarea tratamentului. Un model Markov a fost utilizat pentru a determina cost-eficacitatea utilizării auto-monitorizării INR *versus* monitorizare folosind metode clasice. Am efectuat o analiză a impactului bugetar în cazul în care 1,5% dintre pacienți ar beneficia de auto-monitorizarea INR plătită de Casa Națională de Asigurări de Sănătate. Rezultatele probabile care rezultă din stabilirea pragului de acceptabilitate la 30000 €/QALY, rulând o cohortă cu o vârstă medie de 65 de ani pentru o perioadă de 5 cicluri (5 ani) au condus, în 75% din cazuri, la costul incremental pe unitatea de rezultat suplimentar (ICER) sub pragul de acceptabilitate. Analiza impactului bugetar a arătat că deplasarea a 1,5% din cazurile curente pe autodeterminarea INR va necesita o cheltuială suplimentară în primul an de 813640 EUR. Începând cu anul 5, sistemul de asigurări de sănătate va obține economii progresive de 252419 €. Rezultatele studiului arată că în România auto-monitorizarea INR ar putea fi considerată o intervenție rentabilă și durabilă pentru pacienții care primesc terapie orală anticoagulantă.

Keywords: anticoagulation; cost-effectiveness, budget-impact analysis; INR home testing

Introduction

Venous thromboembolism (VTE) is one of the most common complications that may arise while the patient is hospitalized. Without adequate prophylactic treatment, the incidence of deep VTE is around 10 to 40% in patients with prior medical conditions or undergoing general surgery, and 40-60% after major leg surgery [7]. A meta-analysis performed by Hart *et al*. has shown that the risk of a stroke/systemic embolism for patients with atrial fibrillation is decreased by 64% for those undergoing treatment with K antivitamin (AVK) (warfarin) when compared to placebo [8]. The guidelines recommend using low molecular weight heparins with priority as a prophylaxis against VTE, but in 2015 in Romania there were over 250000 patients undergoing treatment with K antivitamins, acenocoumarol, paid for by the national health insurance system [1]. AVKs have a low therapeutic index, exhibit a variable response, with numerous interactions having been described with foods or with other drugs [5]. The main drawback of AVKs is the need for a strict monitoring of the anticoagulation level in order to avoid either its inefficacy and thus the risk of thrombosis, or excess doses that increase the risk of haemorrhage. After initiating oral anticoagulant treatment, its monitoring is left to the family physician's responsibility, INR testing being performed

monthly in specialized laboratories. The first dedicated services for monitoring patients undergoing oral anticoagulant treatment have come from private healthcare providers, but their costs still vary and they are not being covered by the national health insurance system, thus they were not included in this analysis.

New devices that allow self-monitoring of oral anti-coagulant treatment have led to a lower incidence of complications arising from this treatment, pulmonary thromboembolisms or haemorrhagic strokes which may or may not be followed by death [2, 10, 14].

Despite acknowledging their benefits, European healthcare systems have taken different stances on covering the costs of these devices out of public coffers, particularly due to the initial cost involved in purchasing the device. Many countries have thus performed economic valuations on the cost-efficacy of self-testing/self-monitoring of oral anticoagulants with antivitamins K, as well as the budgetary impact involved in introducing them [2, 12]. As at the time of this analysis, neither devices for self-testing/self-monitoring the International Normalized Ratio (INR), nor the accessories required for testing (test strips, lancing devices, etc.) are covered by the Romanian health insurance system. Given the large differences between the cost of healthcare in Romania and most EU countries, we have conducted this study in order to evaluate the cost-effectiveness of home self-monitoring of anticoagulation with special devices as compared with the classical method of determining the INR as well as an analysis of the budgetary impact of covering the costs of a number of patients for INR self-monitoring, given the particulars of our country.

Although the spectrum of complications arising from oral anticoagulant treatment is broader and also includes minor thrombotic or haemorrhagic strokes, these have been excluded from this analysis. The cost associated with being disabled is also difficult to estimate [4, 13]. Since the paying third party's perspective is dominant (National Health Insurance House's perspective), and most such costs are bearded by the family, the results of the modelling have to be interpreted as referring only to major strokes, and their acute state, respectively, and only data provided by the authorities for cases of acute patients have been taken into consideration, to which the rehabilitation costs in the following years have been added, with the costs arising for cases where the respective illnesses have been considered as secondary diagnoses being ignored.

Furthermore, the economic analysis has not taken into consideration treatment with new oral anti-coagulants, which poses far fewer problems in maintaining a constant INR but it is currently not being reimbursed by the health insurance system and as such does not fit with the chosen perspective.

Materials and Methods

The model. A software developed by Oblikue Consulting s.l. (Spain) has been used for running the model, based on the Markov model as shown in Figure 1 [14].

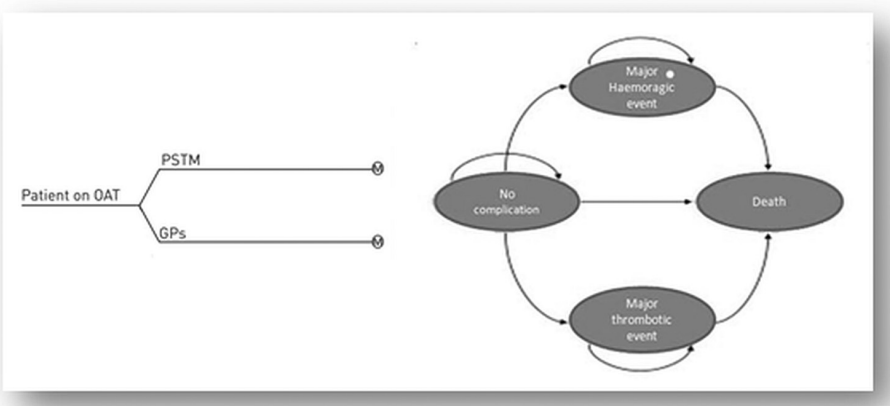

Figure 1.
The Markov model used in the analysis [14]

The data used has been taken from the specialized literature, based on expert opinions as well as epidemiological and cost data (unpublished) provided by the National Health Insurance House (NHIH), the Ministry of Health, and the National Institute for Statistics (NIS), the National School for Public Health, Management and Healthcare Continuous Development (NSPHMHCD).

Within the Markov modelling, patients can fluctuate between four states of health: no complications, major haemorrhagic events, major thrombotic events and death. The rates specific to the age of natural death have been taken from mortality tables provided by the NIS. It was assumed that all patients have initially been in a state of "no complications". The main result was the ratio of incremental cost-

effectiveness with marginal costs as the numerator and incremental health benefits as the denominator. The duration of a cycle was chosen to be one year.

Values used for comparisons. As part of the Markov modelling performed for the economic analysis it was opted to compare self-testing *versus* the usual care provided in such cases by the family physician (FP) and specialists in the ambulatory care. Treatment monitoring is performed on a monthly basis with a referral from the FP to the lab or through one day hospitalization in the hospital where the patient has been diagnosed and has received the prescription for AVKs. Data used in the model is based on expert opinion because the follow-up of these patients is not regulated on a separate basis, with some patients opting to monitor their INR on their own, thus giving up on the free services of the health insurance system. At the other hand, some patients get the benefit of repeated day hospitalizations although they would not really be entitled to them, with a view toward performing other tests apart from the INR. We estimated that patients get, on average, one day of hospitalization each year.

Test subjects. The analysis included all patients that received oral anticoagulant treatment.

The perspective. The analysis was performed taking into consideration the paying entity point of view, thus including as costs only those expenses that the NHIH is reimbursing for this category of patients. As such, only direct medical costs have been used.

Timeframe and discounting rates. The average age of patients undergoing treatment with AVKs was 65 in 2015 (according to the data provided by the NHIH) and the discount rate used was 3%, which was applied to both costs and health results. The cohort was analysed for a 5-year period.

Health outcomes. Results are expressed as life years (LY) and quality-adjusted life-years (QALYs), incremental cost efficacy of self-monitoring when compared with FP monitoring and the budgetary impact of using self-monitoring in the clinical management of patients undergoing oral K anti-vitamin anticoagulant treatment.

Results and Discussion

Probabilities used in modelling. Although the informatics systems allow it, haemorrhages or thromboses arising from anticoagulant treatment are rarely mentioned and coded as such. This is why we have used the probability for these events arising based on data reported by Heneghan *et al*. in 2012 [9]. For each option, the relative risk (RR) that a major haemorrhagic or thrombotic stroke would arise along with death, reported by Heneghan in 2006 and 2012 for ”normal care” (a check-up performed by the FP/self-testing/self-monitoring) has been used to calculate the probability that major complications from that group would appear. The incidence of major complications and death caused by them has been calculated from the specific incidence for hospital units or specialized monitoring centres extracted from meta-analyses adjusted by the relative risk as calculated by Heneghan for the FPs, self-testing and self-monitoring, respectively [9, 10], are presented in Table I.

Table I

The probability of major complications of the specific group calculated based on the relative risk (RR) of major haemorrhagic or thrombotic strokes, as well as death

	Through the FP	Self-testing/Self-monitoring
Major thrombotic event	3.22 (1.50 - 4.94)	1.42 (0.26 - 5.63) RR 0.44 (0.17 - 1.14)
Major haemorrhagic event	2.84 (1.16 - 4.52)	2.58 (0.86 - 5.06) RR 0.91 (0.74 - 1.12)
Death	2.87 (1.01 - 4.74)	2.35 (0.53 - 6.07) RR 0.82 (0.52 - 1.28)

FP = family physicians

Costs and utilities. Costs have been estimated using data from the literature, data published by the NHIH, data reported by Romanian hospitals for services, as well expert opinions. This analysis has taken into account the costs in Romania for self-testing/self-monitoring using CoaguChek® systems, with prices provided by the supplier. The costs expressed in local currency (RON) have been converted to EURO at a rate of 4.5 RON for one EURO.

The costs included in the modelling are those that are usually associated to patient’s monitoring under-going K antivitamin treatment (fees charged by FP’s, materials used, fees charged by the laboratories for determining INR) and fees reimbursed by the NHIH for treatment of diseases (thromboses and haemorrhages) that may arise from K antivitamin treatment (acenocoumarol in this case).

Costs arising from monitoring through the FP include the monthly fee paid by the NHIH for monitoring chronic patients, one consultation in the ambulatory every six months and the cost of the 12 annual testing of the INR (Table II). The FP *per* capita payment has not been included because it is also reflected in the case of self-monitoring.

For self-testing/self-monitoring we took in consideration a specialist consultation in the ambulatory care,

once every 6 months. We considered that training for using the device will come at no additional cost and will be offered by the distributor's sale force. For both monitoring types we have included the maximum price covered by the NHIH for acquiring acenocoumarol. INR and Quick time test (offered only together) are covered up to the amount of €3.26.

Table II

Costs of self-monitoring and the cost of monitoring provided by the FP (family physician). Data taken from the guidelines for applying the health insurance frame contract (data source www.CNAS.ro)

COST OF SELF-TESTING/SELF MONITORING		In the first year	In the following years
CoaguChekdevice cost	€300.00	€300.0	0
Cost of test strip (24/year)	€3.20	€76.8	€76.8
Cost of specialist consultation (2/year)	€4.88	€9.8	€9.8
Medication cost (*per* therapeutic unit x 365)		€4.38	€4.38
Total		**€391**	**€91**
COST OF MONITORING Provided by the FP			
Cost of FP consultations (12/year)	€4.88	€58.7	€58.7
Cost of specialist consultation (2/year)	€4.88	€9.8	€9.8
Cost of INR testing x 12/year	€3.26	€391	€391
Medication cost (*per* therapeutic unit x 365)		€4.38	€4.38
Total		**€112**	**€112**

For the state of major haemorrhagic stroke only costs arising from admissions within one year of the event (one hospitalization in an acute department) have been taken into consideration, assuming that in the following year the patient cannot be allowed to self-monitor due to the risk of a haemorrhage. For serious thromboembolism with stroke without tetraplegia the costs of hospitalization in an acute patient department and two hospitalizations in the recuperating department have been taken into consideration, whereas for the following years the costs corresponded to one hospitalization per each chronic patient per year (€1278.4 + €839 in the first year and €839 in the following years).

The average estimated costs reimbursed by the health insurance system for thrombotic stroke, haemorrhagic stroke and recovery/event were as follows: thrombotic stroke - €748.8, cerebral haemorrhage (vascular haemorrhagic stroke) - €1278.4, neurological medical recovery (€62.88/day average duration 13.34 days) - €839.

Time spent in the different states of the model has been adjusted by the respective utility level reflecting quality of life for different states of health, with 1 being in a state of perfect health and 0 being deceased. Utilities were used for the initial state and major complications using data published by Connok *et al*. in 2007 [3]. The calculation of quality-adjusted life-years (QALYs) was performed using data obtained by calculating utilities at the beginning of monitoring, after 6 months and 12 months as performed by Regier *et al*. in 2006, and by Connock *et al*. in 2007 [3, 11].

In the simplified version of the model, only utilities associated with major complications (thrombotic stroke, temporary ischemic strokes and pulmonary embolism) have been used (Table III). In the absence of national studies and according to the opinion of the experts that have been consulted, the value of the utilities should not differ from those that have been applied in the UK. The model did not include minor haemorrhagic or thromboembolic strokes, considering that the utilities for an entire year do not differ from the "no complications" stage, since the patient is able to make a full recovery.

Table III

Utilities assigned to states considered in the Markov model

Value of utilities	Estimated level	Lower estimate	Upper estimate	Data source
No events- regular care	0.738			Birmingham (SMART) trial [13]
Difference between regular care and self-monitored patient care	0.001	-0.027	0.032	Birmingham (SMART) trial [13]
Major haemorrhagic events.				
Acute stage	0.54	0.44	0.64	Regier *et al*., 2006 [10]
Thromboembolic events				
Acute stage	0.45	0.35	0.55	Regier *et al*., 2006 [10]

Cost Effectiveness Analysis (CEA) - deterministic results

The Table IV includes the average cost *per* patient, life years gained, the cost *per* life year gained and the cost *per* QALY gained when comparing self-monitoring with the current monitoring system being reimbursed by the NHIH (through the FP).

Table IV

Deterministic results for the model extending over a 5-year period

	Cost	LY	C/LYG	QALY	C/QALY
Self-monitoring	€938	4.27		3.07	
Through the FP	€1006	4.22		2.99	
Self-monitoring-FP	-€68	0.05	Dominant	0.09	Dominant

LY = life years gained, QALY = quality-adjusted life-years gained, with the self-monitoring intervention being dominant as much as it generates both a saving, as well as a gain in QALY or life years

Probabilistic outcomes resulting from setting the acceptability threshold of €30000/QALY running a cohort with an average age of 65 for a period of 5 cycles (5 years) has led in 75% of cases to an ICER below the acceptability threshold, with 57% of the results being in the dominant area (Figure 2).

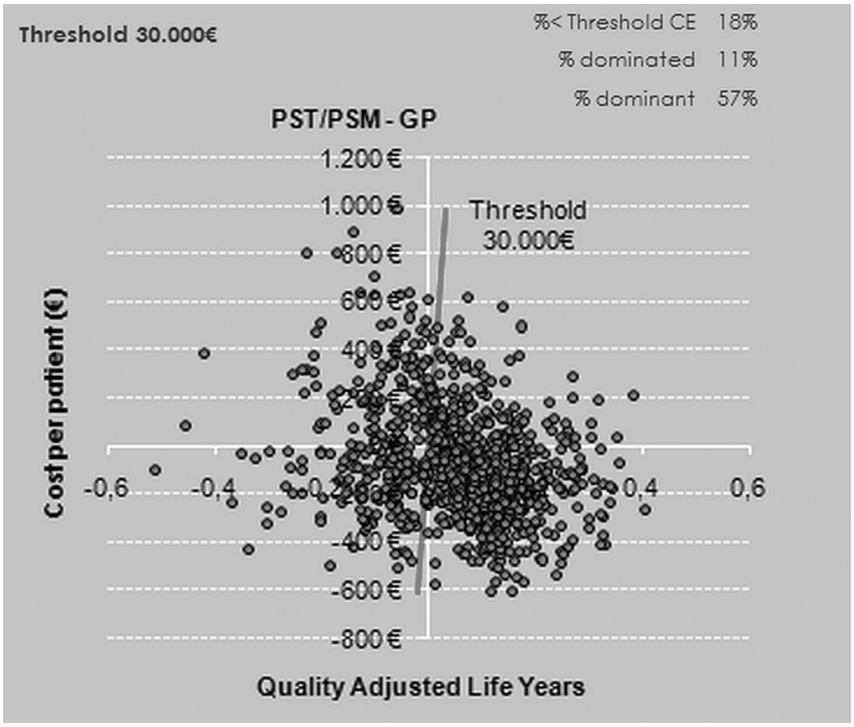

Figure 2.

Probabilistic results for cost-effectiveness chart when comparing self-monitoring versus family physician mediated monitoring (average age of the cohort is 65 years, follow-up time 5 years, cost of the device without consumables €300, threshold chosen €30000 for a QALY)

Budget impact

In order to analyse the budgetary impact, we took into consideration the data from the cost effectiveness study with a hypothetical financing of only 1.5% of patients currently undergoing treatment with oral anticoagulants (according expert's opinion consulted regarding the number of patients suitable for self-monitoring).

According to existing data, NHIH had in its records 248359 patients (single personal ID number) receiving acenocoumarol treatment in 2015. Out of them 74378 received the treatment while being hospitalized.

Table V shows the total costs for patients treated with AVKs in the current scenario, the new scenario and the difference (net impact). The results of the budgetary impact analysis indicate the fact that the change in the current patient distribution, as described, from the current scenario to the new scenario involving self-testing/self-monitoring, will entail a small but positive cost due mostly to the cost of the device, as the chart shows. If, within the first year of the chosen scenario, the system will have additional expenses of €813000, the amount will decrease in the following years to €555000 for the second year, and only €290000 for the third year, while costs would nearly even out compared to the benefits in the fourth year (an additional cost of only €20000). Starting with year 5, the health insurance

system will start earning progressive savings (around €252000).

The premise of the analysis constitutes an uncertainty factor in itself, that is, patients that agree to self-test/self-monitor have better results regarding the incidence of thrombotic and haemorrhagic strokes. It is true that this patient category is assumed to be endowed with a level of understanding that would allow them to use the respective devices. It is expected that these patients, however, be nevertheless more compliant and more inclined to self-monitor the blood coagulation level irrespective of the method used.

Table V

An analysis of budgetary impact over 5 years (in €). Scenario 1 includes 248359 patients undergoing treatment with AVKs, all monitored through the FP, whereas the new scenario applies to the same number of patients, of whom 1.5% will self-monitor (3725 patients)

	1st year	2nd year	3rd year	4th year	5th year
Current scenario (€)	49665270	99868725	150194082	200289465	249859509
New scenario (€)	50478910	100424601	150484489	200309750	249607091
Net cost (€)	813640	555876	290407	20284	-252419

When analysing the budget impact, one must also take into consideration a potential decrease of the number of patients undergoing K antivitamin treatment in case new oral anticoagulant drugs will be funded for some patient categories.

The model has shown a maximum sensitivity towards the cost related to patients with thromboembolic strokes, its likelihood and the self-monitoring device's purchase price.

The model did not include costs related to the treatment of patients that will become disabled, because these costs would tip the scales even further in favour of recommending that self-monitoring be funded by the health insurance system.

Conclusions

The study findings show that in Romania self-monitoring of INR could be regarded as a cost-effective and sustainable intervention for the patients receiving acenocumarol.

Our results did not take into consideration the influence of possible future financing of the new and safer class of anticoagulants.

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