COST-EFFECTIVENESS OF APIXABAN IN PREVENTION OF STROKE AND SYSTEMIC EMBOLISM IN THE CZECH REPUBLIC

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OBJECTIVES

Apixaban is an oral anticoagulant, direct factor Xa inhibitor. The aim of the analysis was to compare costs and effectiveness of apixaban in the first line prevention of stroke and systemic embolism in vitamin K antagonist (VKA) suitable patients with atrial fibrillation (AF). The analysis was conducted from the perspective of the public healthcare payer in the Czech Republic.

METHODS

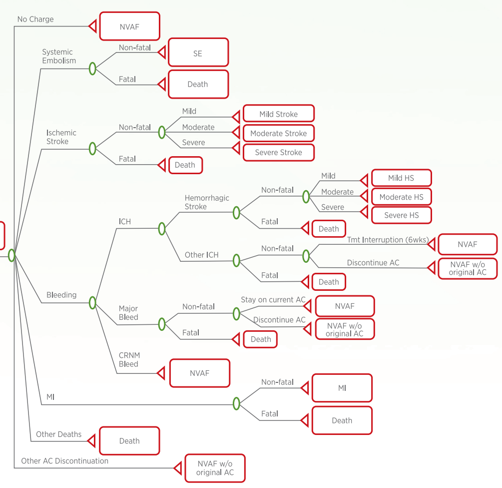
Health-economic model

To assess on cost-utility of apixaban, a Markov model was developed. The analysis was focused on the first line prevention of stroke and systemic embolism in VKA suitable patients suffering from AF with at least one risk factor present (symptomatic heart failure of class II or higher according to NYHA classification, age of 75 years or higher, diabetes mellitus, hypertension).

Apixaban was compared to used and reimbursed intervention (warfarin) in terms of lifetime costs per quality-adjusted life year. All costs and outcomes were discounted at 3 %.

A Markov model was developed in Microsoft Excel using a six week cycle length with the following health states of Non-valvular AF (NVAF): →

Figure 1 • **HE model - health states**



Efficacy

The probability of transition between the individual states is modeled based on the risk of occurrence of the event (ARISTOTLE [1] study was reported per 100 patient-years (PY)) which was converted to 1 day (λ) according to the formula:

$$\lambda = \frac{Hazard\ (per\ 100\ PY)}{(365.25 \times 100)}.$$

The probability of an event occurring during one cycle was then calculated using an exponential model as:

$P(x) = 1 - e^{-\lambda t}$,

where λ means the risk of occurrence of the event converted to one day and one patient, and t means the number of days per cycle (in this case, $t = 42$).

Table 1 • **Hazards per clinical events**

		apixaban	warfarin
Stroke	Hazard (per 100 PY)	0.98051	1.07718
	Hazard (per 1 day)	0.00003	0.00003
	Risk (per cycle)	0.00113	0.00124
ICH	Hazard (per 100 PY)	0.33000	0.80000
	Hazard (per 1 day)	0.00001	0.00002
	Risk (per cycle)	0.00038	0.00092
Other Major Bleed	Hazard (per 100 PY)	1.79000	2.27000
	Hazard (per 1 day)	0.00005	0.00006
	Risk (per cycle)	0.00206	0.00261
CRNM Bleed	Hazard (per 100 PY)	2.08300	2.99500
	Hazard (per 1 day)	0.00006	0.00008
	Risk (per cycle)	0.00239	0.00344
MI	Hazard (per 100 PY)	0.53000	0.61000
	Hazard (per 1 day)	0.00001	0.00002
	Risk (per cycle)	0.00061	0.00070
CV Hospitalization	Hazard (per 100 PY)	10.46000	10.46000
	Hazard (per 1 day)	0.00029	0.00029
	Risk (per cycle)	0.01196	0.01196
Other Tx Discontinuations	Hazard (per 100 PY)	13.17700	14.40500
	Hazard (per 1 day)	0.00036	0.00039
	Risk (per cycle)	0.01504	0.01643
Systemic Embolism	Hazard (per 100 PY)	0.09000	0.10000
	Hazard (per 1 day)	0.00000	0.00000
	Risk (per cycle)	0.00010	0.00011
Other death	Hazard (per 100 PY)	3.08245	3.34036
	Hazard (per 1 day)	0.00008	0.00009
	Risk (per cycle)	0.00354	0.00383

An identical procedure was also used to calculate the risk of recurrent stroke. The risk of recurrent stroke within the cycle was considered for both comparators at 0.003123 (for ischemic and hemorrhagic stroke), which corresponds to a hazard of 2.72 per 100 PY [2].

Mortality

Background mortality

Background mortality is modeled for the first 1.8 years of treatment based on the results of the ARISTOTLE clinical study [1], it is considered at the rate of 3.0825 per 100 PY for patients with apixaban and 3.3404 per 100 PY for warfarin.

The rest of life is modeled by Gompertz curve using mortality tables of the Czech Republic [3].

$\ln(u(t)) = \lambda + \gamma t$,

where u(t) is estimation of mortality in age t, λ = ln(a) and γ = ln(b):

Table 2 • **Background mortality**

	γ	λ
Men, <= 75 yr	0.097784	- 10.2883
Women, <= 75 yr	0.100548	- 11.2084
Men, > 75 yr	0.090070	- 9.7980
Women, > 75 yr	0.119629	- 12.5798

Specific mortality

The increased risk of specific mortality reflects hazard ratios summarized in the following table:

Survival function is as follows: $f = e - \frac{e^{\lambda + \ln(HR)}(e^{\gamma t} - 1)}{\gamma}$,

where t is age of patient.

Table 3 • **Specific mortality**

Event		HR	Source
Stroke/ICH	Mild	3.18	[4], [5], [6]
	Moderate	5.84	
	Severe	15.57	
NVAF		1.34	[7]
Systemic Embolism		1.34	Assumption
MI	Men	2.56	[8]
	Women	4.16	

Quality of life

Utilities for each state is shown in the following table [9]: ←

Table 4 • **Quality of life (utilities)**

State		Utility
NVAF		0.7270
Stroke/ICH	Mild	0.6151
	Moderate	0.5646
	Severe	0.5142
Systemic Embolism		0.6265
MI		0.6098

Utility decrements associated with clinical events and use of anticoagulants is shown in following table [9], [10], [11]: ←

Table 5 • **Quality of life (utility decrements)**

	Utility Decrement	Duration
Clinical events		
Other ICH	0.1511	6 weeks*
Other major bleeds	0.1511	2 weeks
CRNM bleeds	0.0582	2 days
Other CV hospitalisation	0.1276	6 days*
Use of anticoagulant		
Warfarin	0.0130	While on warfarin
NOACs	0.0020	While on NOAC*

*Assumption

Costs

Drug costs, acute care costs and management costs were assumed (March 2017) [12].

Table 6 • **Drug costs**

Drug	Average daily dose (mg)	Average drug costs per day	Average drug costs per cycle
Apixaban	10	2.33 EUR	97.86
Warfarin	7.5	0.10 EUR	4.31

Costs associated with clinical events [13], [14], [15] varies between 1312.99 EUR and 3506.68 EUR per episode for acute care and 5.44 EUR and 118.19 EUR per month for maintenance treatment.

Yearly management costs (renal monitoring and dyspepsia) are 39.04 EUR and 42.30 EUR for apixaban and warfarin respectively [1], [13].

RESULTS

In the base case scenario, the incremental cost-effectiveness ratio (ICER) of apixaban compared to warfarin reached 18074 EUR/QALY. QALYs and LYs gained on apixaban treatment were 6.035 and 8.465 whereas patients on warfarin treatment gained only 5.851 and 8.288.

Moreover, apixaban prevented the occurrence of adverse events as it reduced the number by 87 (measured per 1000 patients).

Figure 2 • **ICER vs WTP**

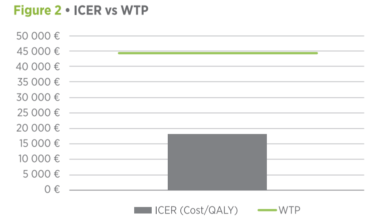
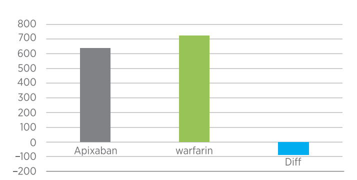
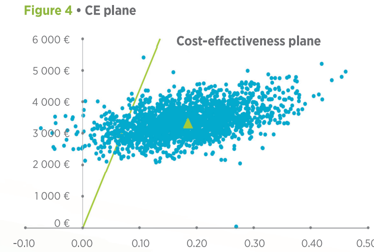


Figure 3 • **Number of events - API vs warfarin**



The probabilistic analysis of sensitivity showed that 92 % of iterations are located below the willingness to pay threshold

Figure 4 • **CE plane**



CONCLUSION

Based on the results apixaban prolongs total survival and improves quality of life of VKA suitable patients with atrial fibrillation. Use of apixaban decreased the occurrence of cardiovascular events. Results indicate apixaban treatment is also very cost-effective as the ICER stays well below willingness to pay threshold (44 390 EUR).

Disclosure

This analysis was supported by Pfizer s.r.o.

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