

Cost-Effectiveness Analysis of different anticoagulant classes in Cancer Associated Thrombosis (CAT)

A differential approach accounting Thrombotic and Bleeding risk, applied in the Greek Health Care environment.

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ABSTRACT

Background: Guidelines recommend that Cancer-associated thrombosis (CAT) should be treated with low-molecular weight heparins (LMWH), which prevent more effectively the recurrence of Venous Thrombo-Embolism (VTE) than Vitamin K Antagonists (VKA). New Direct Oral Anti-coagulants (DOAC) may be more convenient and have been recently tested against LMWH in CAT patients.

Objective: Assess the cost effectiveness of the different anticoagulant classes in CAT in the Greek Healthcare (HC) setting from the hospital perspective, accounting different bleeding/thrombotic Risk groups (High/Low) defined by presence of chemotherapy/metastasis.

Methods: Markov chain modeling accounting VTE, Major Bleeding (MB), clinically relevant non-major bleeding (CRB) and death as major states, incorporating additional mortality risk by VTE and MB. All comparisons were made versus (vs) VKA as base. All costs were derived in the context of the Greek HC system and included direct pharmacological costs, Diagnosis Related Group (DRG) costs for the management of VTE, MB, CRB and secondary support costs of VKA (laboratory testing and HC professionals consultation visits).

Results: For Low Risk CAT patients DOAC were more cost effective in all analyzed endpoints (VTE, MB, CRB) including Life Years Gained (LYG) and total Utility with a favorable estimated Incremental Cost-Effectiveness Ratio (ICER) of less than €300 per LYG or per Quality Adjusted Life Year (QALY) gained vs VKA. In High Risk CAT patients DOACs were dominated by VKA in QALY, LYG, MB and CRB with negative ICER values, making LMWH acceptably cost effective option (ICER of €15.000 per LYG and €22.000 per QALY gained vs DOAC).

Conclusions: Risk stratification for CAT patients might prove useful achieving higher cost effectiveness from the different anticoagulant classes. For the Greek HC environment, DOAC seem more cost effective for the Low Risk CAT patients, while LMWH deem preferred for High Risk CAT patients offering acceptable cost-utility gains.

1. BACKGROUND

Cancer patients are exposed to a 5-7 fold increased risk for Venous Thrombo-Embolism (VTE), developing up to 15% symptomatic VTE and having cancer contributing for up to 18% of all cases of VTE.¹⁻⁵

Cancer Associated Thrombosis (CAT) affects patient's quality of life^{6,7} and is connected by cancer type, stage, and time since diagnosis⁸ with clotting risk being highest in the first three to six months after cancer diagnosis.⁹ Administration of chemotherapy has been shown to be a factor that further increases the risk for VTE with recorded incidence rates that may reach up to 13.5% following therapy initiation.¹⁰

Clinical studies have demonstrated that cancer patients on active treatment who develop VTE should receive therapy using low-molecular weight heparin (LMWH), which prevents more effectively the recurrence of VTE than Vitamin K Antagonists (VKA)¹¹⁻¹³, a previous generation oral anti-coagulation option, requiring frequent monitoring (INR) and dose adjustments to maintain stable plasma levels.

International guidelines recommend that CAT should be treated with LMWH for at least three to six months¹⁴⁻¹⁶ and clinical documentation demonstrates that LMWH do not increase the rates of major (MB) or clinically relevant non-major bleeding (CRB) compared with the long term use of VKA.^{11,13}

Direct Oral Anti-coagulants (DOAC) have been tested against VKA in non-cancer VTE patients showing a favorable profile in terms efficacy and safety without the additional costs of frequent laboratory testing and dose adjustment inconvenience that VKA incurs.¹⁷

In post hoc, sub-group analysis of DOACs registration trials, the small portion of CAT patients included, revealed a similar or even favorable profile versus VKA, indicating a possible valuable option for adopting a single oral anticoagulant solution in CAT.¹⁸

Network meta-analysis of DOACs versus LMWH in CAT patients (based on cross-comparisons versus VKA base) indicate similar safety and effectiveness profile²¹, nevertheless these comparisons are extrapolated by different VTE and MB patient risks, therefore their acceptance remains limited in the actual clinical practice setting and guidelines.^{10,19}

LMWH versus VKA trials (and all their meta-analysis) reflect, in general, a higher risk CAT population in terms of factors affecting thrombosis and bleeding risk (mostly related to higher percentages of metastatic patients that may reach up to 67% and higher percentages of patient under chemotherapy reaching up to 78%^{11,13}) while DOAC versus VKA trials sub-group comparisons (and all their meta-analysis) reflect a lower risk CAT population (e.g. metastasis ranging from 13-33% and systemic therapy up to 31%^{18,24-26}).

Current adherence to LMWH treatment guidelines remains lower than expected, having VKA being still used in considerable rates, and DOAC being used as an alternative option either replacing VKA for monitoring reasons or LMWH for cost or patient preference reasons.²⁰

Published cost effectiveness comparisons indicate that long term LMWH in CAT is a cost-effective option at a range of €8.000-27.000 per avoided VTE, and €5.000-15.000 per QALY gained among various health care settings in Europe and Canada.²¹ Nevertheless no clear analysis has evaluated so far, the cross comparisons of DOACs versus VKA and LMWH represented as different (class) options in CAT management.

Recently published evidence comparing DOAC versus LMWH in high risk population (metastasis and chemotherapy) along with their meta-analysis indicates that DOAC might be even more efficacious than LMWH in terms of VTE (risk reduction near 35%) but considerably less safe in terms of MB and nm-CRB (risk increase of +74% and +131% respectively).¹⁹

2. OBJECTIVE & HYPOTHESES

Based on the recently published clinical trials, the objective of the current dissertation is to assess the cost effectiveness of different anticoagulant classes in the long term (6 months anti-coagulation) CAT management in the Greek Healthcare setting.

The assessment will be from the hospital perspective, accounting 2 different bleeding and thrombotic risk groups, and will produce different comparative and sensitivity analysis results for DOAC and LMWH versus VKA management, testing the hypothesis that LMWH (current standard of care) will deem more appropriate to be used only in the higher thrombotic & bleeding risk CAT patients (metastasis/chemotherapy) while DOAC will deem more appropriate to be used in lower thrombotic & bleeding risk CAT patients

3. METHODS

Although LMWH and DOAC brands are not considered interchangeable, relatively limited safety and efficacy differences arise amongst the different brands within their classes. For the purpose of the current analysis DOAC and LMWH would be considered as classes with consolidated safety and efficacy results per class, and various cost analytics would apply in sensitivity analysis base for possible brand differentiation after model implementation.

Methodology would consist by constructing a simplified Markov model evolving in monthly cycles, with the following states: Thrombo-prophylaxis (receiving an anticoagulant to prevent VTE), MB, VTE, CRB and Death (Diagram 1) and by defining the monthly transition probabilities between each state for each class and each risk level (matrix algebra). VKA (base) probabilities would be calculated by exponential distribution ($p=1-e^{-rt}$) of relative published event rates (clinical data). LMWH and DOAC probabilities would be a product of VKA base calculations by

published Risk Ratios (RR) or by disease modelling RR. LMWH and DOAC monthly probabilities lacking published or modelled RR, would be derived in similar to VKA (event to probability) exponential methodology from relative published trials.

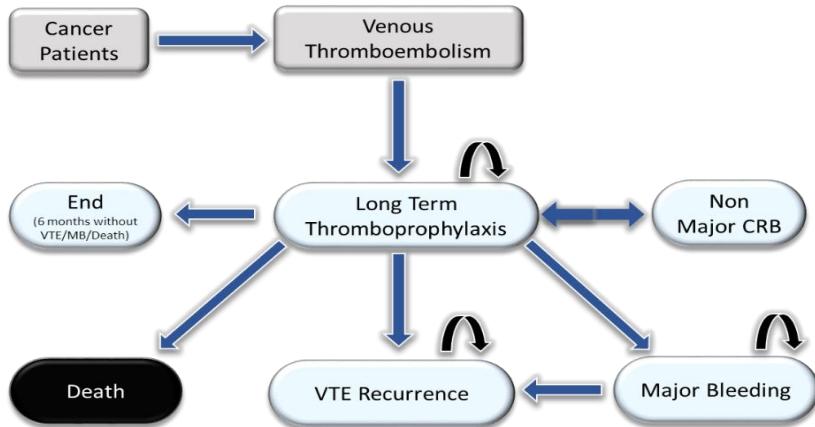


Diagram 1: Applicable Markov Model estimating VTE, MB, CRB and Death as health states

Published meta-analysis^{17-19,22} comparing these agents in prevention of recurrent VTE, safety (MB, CRB) and mortality (MOR), accounting the different level of patient risk population can be summarized in the demonstrated RR of table 1 below:

Patient Type	LMWH vs VKA				DOAC vs VKA				DOAC vs LMWH			
	VTE RR	MB RR	CRB RR	MOR RR	VTE RR	MB RR	CRB RR	MOR RR	VTE RR	MB RR	CRB RR	MOR RR
High Risk CAT	0,60	1,08							0,65	1,74	2,31	1,03
Low Risk CAT					0,65	0,72						
non-Cancer VTE	0,82	0,5			0,96	0,59	0,80					

Table 1: Published Risk Reduction ratios (RR) of different anticoagulant classes in long term cancer and non-cancer thrombosis treatment.^{17-19,22}

Applying simplified indirect methodology for estimating DOAC vs VKA results in High Risk CAT group we can extrapolate the RR for VTE, MB and CRB as a product of already known relative Risk Ratios of LMWH (vs VKA) and DOAC (vs LMWH) following the equation below:

$$RR_{(DOAC \text{ vs } VKA) \text{ High Risk CAT}} = RR_{(DOAC \text{ vs } LMWH) \text{ High Risk CAT}} \times RR_{(LMWH \text{ vs } VKA) \text{ High Risk CAT}}$$

Similarly, and since no comparisons of LMWH vs VKA in low CAT risk patients have been published, we can follow the assumptions of

- a) increasing efficacy (VTE) differences with increasing VTE risk and
- b) decreasing safety (MB) differences with increasing VTE risk

Both assumption have been verified in DOAC and LMWH from the RR of their non-cancer VTE^{17,22} to the RR of the CAT patients^{18,19} and therefore the estimated Low Risk RR of LMWH vs VKA (VTE, MB) may be chosen as a simplified average function by the equation below:

$$RR_{(LMWH \text{ vs } VKA) \text{ Low Risk CAT}} = \frac{1}{2} RR_{(LMWH \text{ vs } VKA) \text{ High Risk CAT}} + \frac{1}{2} RR_{(LMWH \text{ vs } VKA) \text{ non-Cancer VTE}}$$

Clinical Relevant non major bleeding (CRB) and mortality RR of LMWH vs VKA in low risk CAT patients will be assumed equal to DOAC vs VKA and the remaining mortality ratios will be calculated via probability modeling based on the incidence of events in the meta-analysis of their relevant trials (tables A1 & A2 Appendix for Low and High risk accordingly).

Implementing all the aforementioned assumptions, the following Risk Ratio matrix is produced and is applicable for the different anticoagulant classes in the different CAT risk levels (table 2):

Patient Type	LMWH vs VKA				DOAC vs VKA				DOAC vs LMWH			
	VTE RR	MB RR	CRB RR	MOR RR	VTE RR	MB RR	CRB RR	MOR RR	VTE RR	MB RR	CRB RR	MOR RR
High Risk CAT	0,60	1,08	0,73	0,98	0,39	1,88	1,69	1,01	0,65	1,74	2,31	1,03
Low Risk CAT	0,71	0,79	0,92	0,90	0,65	0,72	0,92	0,90				
non-Cancer VTE	0,82	0,5			0,96	0,59	0,80					

Table 2: Estimated Risk Reduction (RR) ratios of different anticoagulant classes in long term cancer thrombosis treatment. Grey box RR refer to indirect (network) estimations. Black box RR refer to disease modelling. Orange box RR are calculated by event related probability calculations (tables A1 & A2 appendix).

Bleeding and VTE risk is correlated mostly in the first 6 months and while under anticoagulation according available studies duration, therefore the simulation will be set to run in 2 stages. First stage will be the first 6 cycles (months) period for emerging VTE/MB & CRB and second stage will expand up to 60 months in order to allow adequate timeframe for utility and survival estimations, accounting only relative death probabilities.

VTE and MB events may prove fatal and subsequently affect mortality of the cohort.²³ Based on real world data by RIETE VTE registry the mortality rates of recurrent Pulmonary Embolism (PE) in CAT patients may reach up to 35% (with PE recurrences representing 48% of total VTE, thus morality rate may reach ~17% over recurrent VTE), while fatal bleeding may occur nearly at 28% after recent MB.²³

In order to create a more accurate mortality estimations, the initially calculated monthly mortality probabilities (data in clinical trial environment) will be considered mostly cancer (CA) related and therefore the estimated monthly mortality probabilities would be additionally adjusted according VTE and MB incidence of each cycle based on the equation below:

$$P_{\text{Total Mortality}} = P_{\text{CA related Mortality}} + P_{\text{VTE projected Mortality}} + P_{\text{MB projected Mortality}} \rightarrow$$

$$P_{\text{Total Mortality}} = P_{\text{CA Mortality}} + (P_{\text{VTE death}} * P_{\text{VTE event}}) + (P_{\text{MB death}} * P_{\text{MB event}}) \rightarrow$$

$$P_{\text{Total Mortality}} = P_{\text{CA Mortality}} + (1-e^{-0.17}) * P_{\text{VTE event}} + (1-e^{-0.28}) * P_{\text{MB event}}$$

Applying the aforementioned methodology on the events recorded in VKA, DOAC and LMWH arms^{17-19,24-29} the monthly probabilities for all event types & classes are summarized in table 3 and will be applicable as monthly probability matrix for stage 1 Markov model (table B1 appendix)

HIGH RISK	rVTE	MB	CRB	Ca MORT	F-rVTE	F-MB	Total MOR
VKA	0,0220	0,0109	0,0320	0,0878	0,0035	0,0027	0,0940
DOAC	0,0086	0,0203	0,0541	0,0884	0,0014	0,0050	0,0947
LMWH	0,0132	0,0117	0,0234	0,0858	0,0021	0,0028	0,0908
0							
LOW RISK	rVTE	MB	CRB	Ca MORT	F-rVTE	F-MB	Total MOR
VKA	0,0101	0,0070	0,0213	0,0284	0,0016	0,0017	0,03177
DOAC	0,0066	0,0050	0,0197	0,0256	0,0010	0,0012	0,02788
LMWH	0,0071	0,0055	0,0197	0,0256	0,0011	0,0014	0,02808

Table 3: Estimated monthly event probabilities of each state in different patient risk levels of CAT per anticoagulant class.^{17-19,24-29} F-rVTE & F-MB refer to additional mortality probabilities derived by VTE or MB recurrence.

For stage 2, emerging VTE, MB, CRB events and the anticoagulant exposure will be ceased. All VTE/MB/CRB events and all costs will be compared in the 6-month period, while survival and utility will be assessed in the end of stage 2 level (5 years). After the 6th cycle only the relative probabilities of CA related mortality (Ca MORT) will be applied per anticoagulant and risk level cohort for survival estimation (table B2, appendix). In order to allow accurate utility estimations of the MB/VTE/CRB states, these will be assumed to resolve within one year, and therefore the subsequent, after 6-month, VTE/MB/CRB states will be assumed to erode by 95% within the next half a year (p=30% maintenance per month for each event by exponential calculation table B2, appendix).

On the utility side (table 4), recent research has indicated that the detrimental effect of recurrent VTE in cancer patients reaches nearly -0.075, while MB and CRB reaches -0.052 and -0.023 respectively, starting from a relative low base case (cancer patient utility at initial thrombosis presentation with no further events) of 0,645.⁷

	Initial CAT	r-VTE	MB	CRB
Utility	0,645	0,570	0,593	0,622

*Table 4: Published patient utility functions per event type (VTE, MB, CRB) after initial CAT manifestation and further anticoagulation of 6 months according guidelines.*⁷

The full 60 cycle estimated events of the markov cohort (High risk, Low risk, tables C1,C2,C3 appendix) would be subject to the aforementioned utilities in order to estimate a simplified utility function per Risk Level (60 months) per different anticoagulant class (LMWH, DOAC, VKA) and allow comparisons (tables D1, D2, D3 appendix). The published CRB utility will be applied to the accumulated CRB events (similar to VTE and MB) and the initial CAT utility to those alive without any event.

On the cost side and in order to analyze cost-effectiveness the following major cost elements will be included in the analysis (6 months period):

- a) Direct pharmacological costs for Thromboprophylaxis, as average per class (table 5), accounting LMWH lead in requirement (estimated at 5 days) and SmPC dosing of different anticoagulant agents (average patient weight of 75kg, tables E1 & E2 appendix³⁰⁻³⁷)

Anticoagulant Class	Agent	DDD Cost (month 1, incl Lead In)	DDD Cost (month 1)	DDD Cost (month 2-6)	SmPC dosing (month 1)	SmPC dosing (month 2-6)	LMWH Lead In Required	LMWH (5d) Lead In Cost	
LMWH	Tinzaparin	7,60 €	7,60 €	7,60 €	175IU/Kg/24h	NA	-	€	
	Enoxaparin	5,95 €	5,95 €	5,95 €	100mg/kg/12h	NA	-	€	
	Dalteparin	5,02 €	5,02 €	4,27 €	200IU/kg/day 150IU/kg/day	NA	-	€	
	Class Average	6,19 €	6,19 €	5,94 €					
DOAC	Rivaroxaban	3,65 €	3,65 €	1,99 €	15mg/12h (21d)	15mg/24h	No	-	€
	Apixaban	2,31 €	2,31 €	2,65 €	5mg/12h (14d)	5mg/24h	No	-	€
	Dabigatran	2,45 €	1,70 €	1,70 €	150mg/12h		Yes	30,9 €	
	Edoxaban	2,50 €	1,77 €	1,77 €	60mg/24h		Yes	30,9 €	
	Class Average	2,73 €	2,36 €	2,03 €					
VKA	Sintrom	1,11 €	0,08 €	0,08 €	4-8mg/24h		Yes	30,9 €	
	Panwarfin	1,15 €	0,12 €	0,12 €	2-10mg/24h		Yes	30,9 €	
	Class Average	1,13 €	0,10 €	0,10 €					

NA: Not accounted as LMWH cost is already included

Table 5: Estimated average Defined Daily Dose (DDD) costs of long term CAT treatment in different anticoagulant classes applicable to Greek HealthCare system in hospital selling prices. ³⁰⁻³⁷ Adopted from galinos.gr Greek healthcare pricing & SmPC database

- b) Secondary support cost of VKA treatment (table 6) that include INR laboratory testing and HCP consultation visits.³⁸

VKA Secondary Costs					
Month	Unit Cost INR	Quantity	Unit Cost HCP visit	Quantity	Total (30d)
1		5		3	90,0 €
2		4		2	68,0 €
3	12,0 €	2	10,0 €	1	34,0 €
4		2		1	34,0 €
5		1		1	22,0 €
6		1		0	62,0 €

Table 6: Estimated secondary support costs of VKA treatment in the Greek HealthCare system.³⁸ 15 INR measurements are estimated to be made throughout 6 months period. HCP visits are based on published Time to Treatment Range (INR:2-3) ratio (TTR) for CAT patients (approx. 50%).^{11,13}

- c) Diagnosis Related Group (DRG) costs recorded in the Greek health system³⁹ (table G appendix) for the management of VTE, MB and CRB events (table 7).

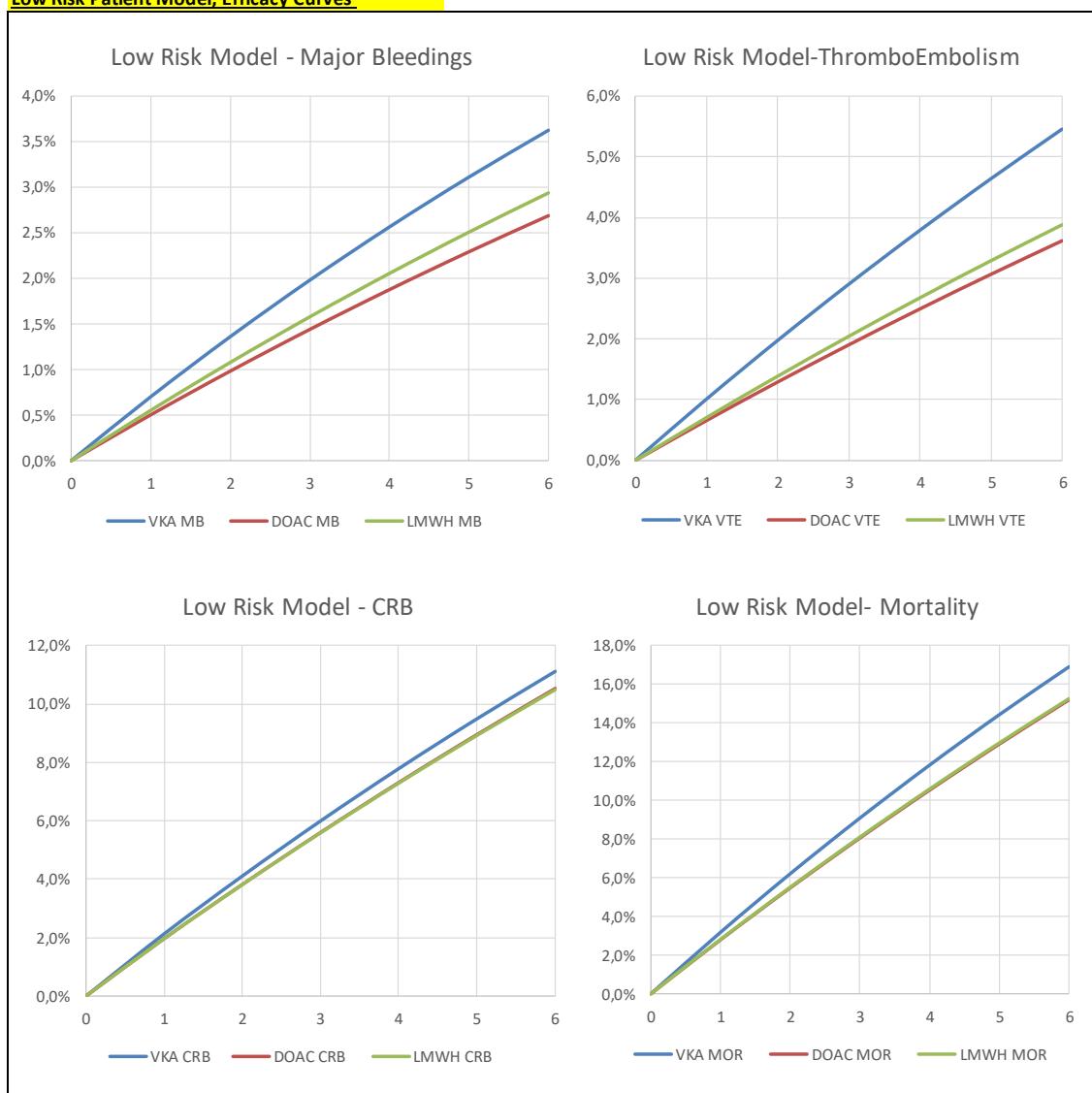
	PE	DVT	VTE (Avg)	MB	CRB
DRG Related Costs	1.988,0 €	1.377,0 €	1.682,5 €	934,0 €	375,0 €

Table 7: Estimated average event costs in CAT treatment applicable to the Greek HealthCare system.³⁹

4. RESULTS

The implementation of the Markov model in the preselected events types (VTE, MB, CRB & Death) for the first 6-months period reveals 2 different and distinct behaviors of the anticoagulant classes over Low and High risk CAT patients (diagram 2 and diagram 3).

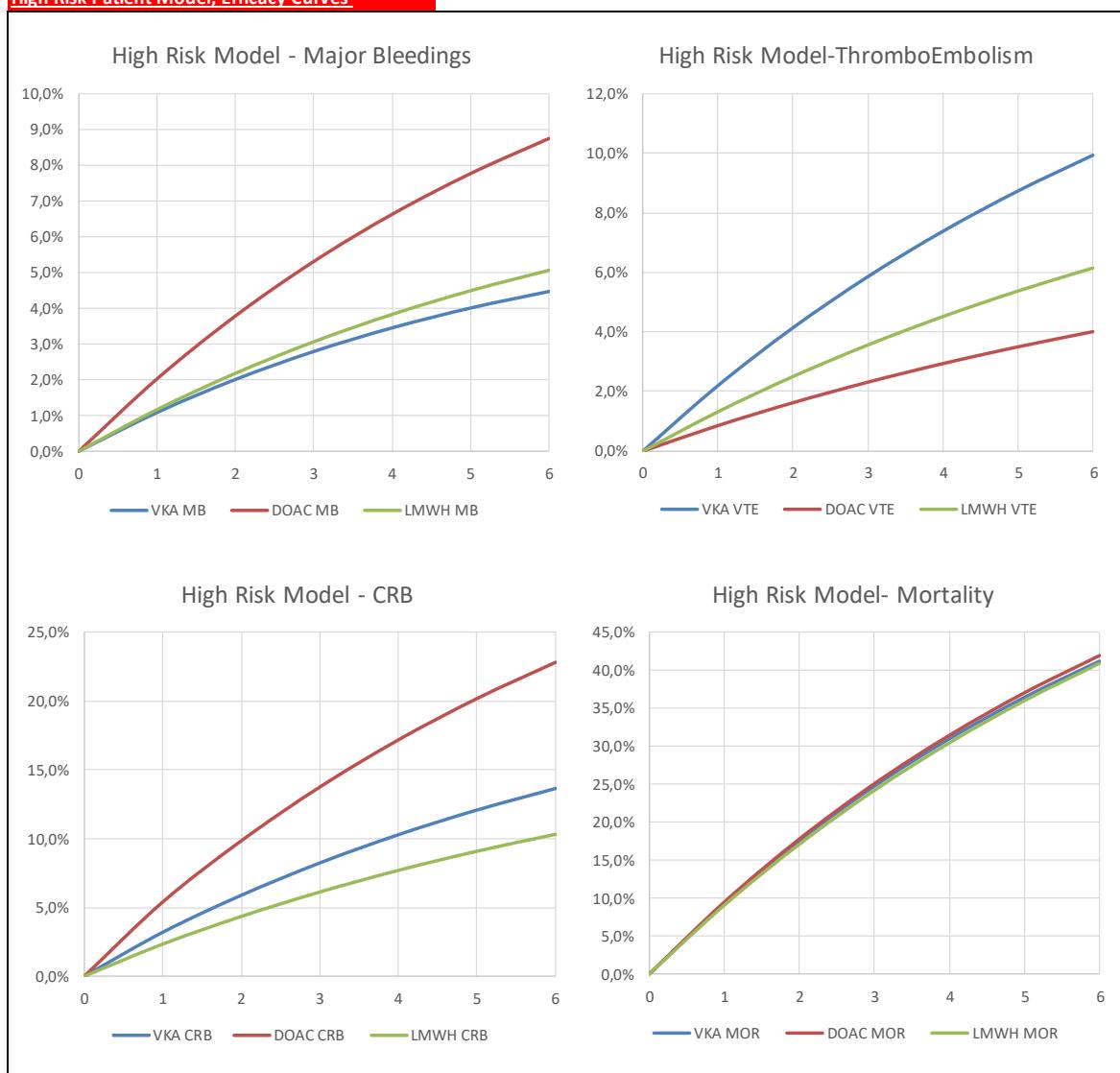
Low Risk Patient Model; Efficacy Curves



Month	LR - Major Bleeding			LR - VTE Recurrence			LR - Clinical Relevant Bleeding			LR - Mortality		
	VKA MB	DOAC MB	LMWH MB	VKA VTE	DOAC VTE	LMWH VTE	VKA CRB	DOAC CRB	LMWH CRB	VKA MOR	DOAC MOR	LMWH MOR
0	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%
1	0,7%	0,5%	0,6%	1,0%	0,7%	0,7%	2,1%	2,0%	2,0%	3,2%	2,8%	2,8%
2	1,4%	1,0%	1,1%	2,0%	1,3%	1,4%	4,1%	3,8%	3,8%	6,2%	5,5%	5,5%
3	2,0%	1,4%	1,6%	2,9%	1,9%	2,0%	6,0%	5,6%	5,6%	9,1%	8,0%	8,1%
4	2,6%	1,9%	2,1%	3,8%	2,5%	2,7%	7,8%	7,3%	7,3%	11,8%	10,5%	10,6%
5	3,1%	2,3%	2,5%	4,6%	3,1%	3,3%	9,5%	9,0%	8,9%	14,4%	12,9%	12,9%
6	3,6%	2,7%	2,9%	5,5%	3,6%	3,9%	11,1%	10,5%	10,5%	16,9%	15,2%	15,2%

Diagram 2: Markov model estimates for accumulated VTE, MB, CRB and Death events after 6 cycles of 3 different anticoagulation classes (VKA, DOAC & LMWH) in **Low Risk CAT** patients.

High Risk Patient Model; Efficacy Curves



Month	HR - Major Bleeding			HR - VTE Recurrence			HR - Clinical Relevant Bleeding			HR - Mortality		
	VKA MB	DOAC MB	LMWH MB	VKA VTE	DOAC VTE	LMWH VTE	VKA CRB	DOAC CRB	LMWH CRB	VKA MOR	DOAC MOR	LMWH MOR
0	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%	0,0%
1	1,1%	2,0%	1,2%	2,2%	0,9%	1,3%	3,2%	5,4%	2,3%	9,4%	9,5%	9,1%
2	2,0%	3,8%	2,2%	4,1%	1,6%	2,5%	5,9%	9,9%	4,4%	17,6%	17,8%	17,1%
3	2,8%	5,3%	3,1%	5,9%	2,3%	3,6%	8,3%	13,8%	6,1%	24,8%	25,0%	24,2%
4	3,5%	6,6%	3,8%	7,4%	2,9%	4,5%	10,3%	17,2%	7,7%	31,0%	31,4%	30,5%
5	4,0%	7,8%	4,5%	8,7%	3,5%	5,4%	12,1%	20,2%	9,1%	36,5%	37,0%	36,0%
6	4,5%	8,8%	5,1%	10,0%	4,0%	6,1%	13,7%	22,8%	10,3%	41,2%	41,9%	40,9%

Diagram 3: Markov model estimates for accumulated VTE, MB, CRB and Death events after 6 cycles of 3 different anticoagulation classes (VKA, DOAC & LMWH) in **High Risk CAT** patients.

The behavior is mostly related to the difference of starting risk per patient profile (VKA control group) combined with the different safety, efficacy and mortality profile of each anticoagulant class per CAT risk level.

High risk patients have an almost double VTE risk under the control (VKA) anticoagulation and significantly higher mortality verifying the assumption of modeled behavior, while the base MB and CRB risk seem to be less affected within the different risk groups for VKA (approx. +25%).

The model output shows that, for the High Risk patients, DOAC are characterized by higher efficacy (VTE) but lower safety (MB & CRB) versus both VKA and LMWH, while in Low Risk patients DOAC are characterized by an improved profile in all safety and efficacy endpoints versus VKA, and their improved safety profile remains (although in slighter degree) also over LMWH (table 8).

Patient Type	VTE			MB			CRB			MOR		
	VKA	DOAC	LMWH	VKA	DOAC	LMWH	VKA	DOAC	LMWH	VKA	DOAC	LMWH
CAT High Risk	10,0%	4,0%	6,1%	4,5%	8,8%	5,1%	13,7%	22,8%	10,3%	41,2%	41,9%	40,9%
CAT Low Risk	5,5%	3,6%	3,9%	3,6%	2,7%	2,9%	11,1%	10,5%	10,5%	16,9%	15,2%	15,2%

Table 8: Estimated event rates (VTE, MB, CRB & MOR) at 6 months under different anticoagulation classes (VKA, DOAC & LMWH) in High or Low Risk of CAT patients .

In a preliminary assessment (excluding costs), DOAC seem to offer a better all-around profile for Low risk patients in all safety/efficacy/mortality end points against all other anticoagulant classes (VKA & LMWH) while in the high risk patient group the image is more complicated due to the increased bleeding (over all classes) and mortality risk (over LMWH) of the DOAC class profile.

Cost analysis also reveals significant differences per anticoagulant class and risk level (tables F1 & F2 appendix; based on stage1 Markov cohorts per monthly cycle).

For a Low risk CAT patient, VKA and DOAC were found significantly less costly than LMWH (-59% and -57% respectively, table 9) while the main cost contributor per anticoagulant class was the drug cost for DOAC (73%) and LMWH (88%) and the secondary medical support costs (INR monitoring and HCP visits) for VKA (52%, diagram 4).

LOW RISK COHORT - COSTS ANALYSIS SUMMARY						
Comparator	Drug Thrombo-prophylaxis	Secondary Medical Support	Major Bleeding (MB)	Venous Thrombo Embolism (VTE)	Clinically Relevant Bleeding (CRB)	Total
VKA	44 €	225 €	34 €	92 €	42 €	437 €
DOAC	338 €	- €	25 €	61 €	40 €	463 €
LMWH	934 €	- €	28 €	65 €	39 €	1.066 €

Table 9: Cost Analysis and contributing elements of different anticoagulation classes (VKA, DOAC & LMWH) in a **Low Risk CAT patient** under 6 months of anticoagulation

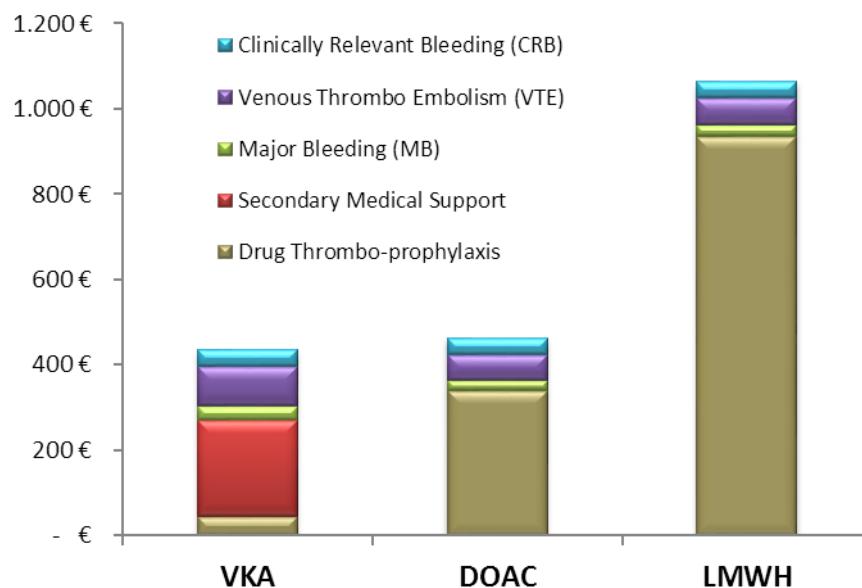
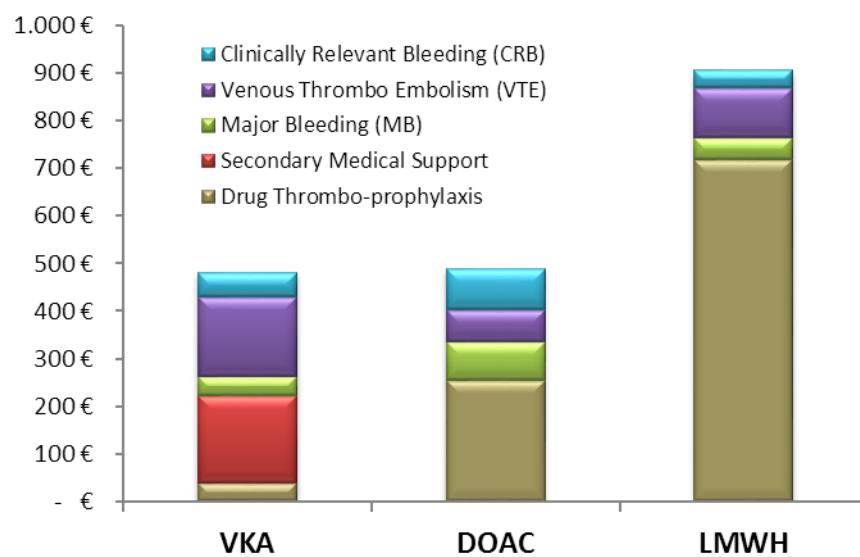


Diagram 4: Cost build-up of different anticoagulation classes (VKA, DOAC & LMWH) for a **Low Risk CAT patient** under 6 months of anticoagulation

For a High risk CAT patient, VKA and DOAC were also found less costly than LMWH (-47% and -46% respectively, table 10) but in a lesser degree than low risk patients mainly as a result of higher VTE and bleeding risk.

HIGH RISK COHORT - COSTS ANALYSIS SUMMARY						
Comparator	Drug Thrombo-prophylaxis	Secondary Medical Support	Major Bleeding (MB)	Venous Thrombo Embolism (VTE)	Clinically Relevant Bleeding (CRB)	Total
VKA	38 €	182 €	42 €	167 €	51 €	482 €
DOAC	254 €	- €	82 €	68 €	86 €	489 €
LMWH	717 €	- €	47 €	103 €	39 €	907 €

*Table 10: Cost Analysis and contributing elements of different anticoagulation classes (VKA, DOAC & LMWH) in a **High Risk CAT patient** under 6 months of anticoagulation*



*Diagram 5: Cost build-up of different anticoagulation classes (VKA, DOAC & LMWH) for a **High Risk CAT patient** under 6 months of anticoagulation*

The main cost contributors in the High risk level for the DOAC class was the drug (52%) and bleedings costs (31%) while for LMWH the main cost contributor remained the drug cost (79%). Very interestingly and due to the high VTE risk the main cost contributors for the VKA class were not only the secondary medical support costs (38%) but also the VTE related cost (35%, diagram 5).

Combining the cost and major events differences (VTE, MB, CRB, Death; as derived from the Markov modeling) the Incremental Cost Effectiveness Ratios (ICER) reveal very distinct behaviors of the anticoagulant classes for the two risk levels. More specifically for the Low Risk CAT group, DOAC are characterized with significantly lower ICER values than LMWH (Table 11).

Comparator	VTE	MB	CRB	Dead	Cost
VKA	5,5%	3,6%	11,1%	16,9%	437 €
DOAC	3,6%	2,7%	10,5%	15,2%	463 €
LMWH	3,9%	2,9%	10,5%	15,2%	1.066 €

Comparator	Δ VTE	Δ MB	Δ CRB	Δ Death	Δ Cost
DOAC vs VKA	1,85%	0,93%	0,59%	1,72%	26 €
LMWH vs VKA	1,57%	0,68%	0,03%	1,65%	629 €

Comparator	ICER VTE Avoided	ICER MB Avoided	ICER CRB Avoided	ICER Death Avoided
DOAC vs VKA	1.426 €	2.837 €	4.427 €	1.532 €
LMWH vs VKA	39.943 €	92.728 €	2.010.751 €	38.027 €

*Table 11: Incremental Cost-Effectiveness Analysis of different anticoagulation classes (DOAC & LMWH) versus VKA in a **Low Risk CAT patient** under 6 months of anticoagulation*

This favorable DOAC cost-effective behavior is based on the relatively small increase in total calculated costs vs VKA (nearly +6% or +€26) and an improved profile in all safety/efficacy and projected mortality event rates.

On the other side, LMWH benefits in event rates are not significantly altered over those achieved by DOAC, but are achieved at a considerable increase of the total associated cost over the VKA therapy (+144% or +€629) verifying a less cost-efficient behavior than DOAC (vs VKA base; diagram 6)

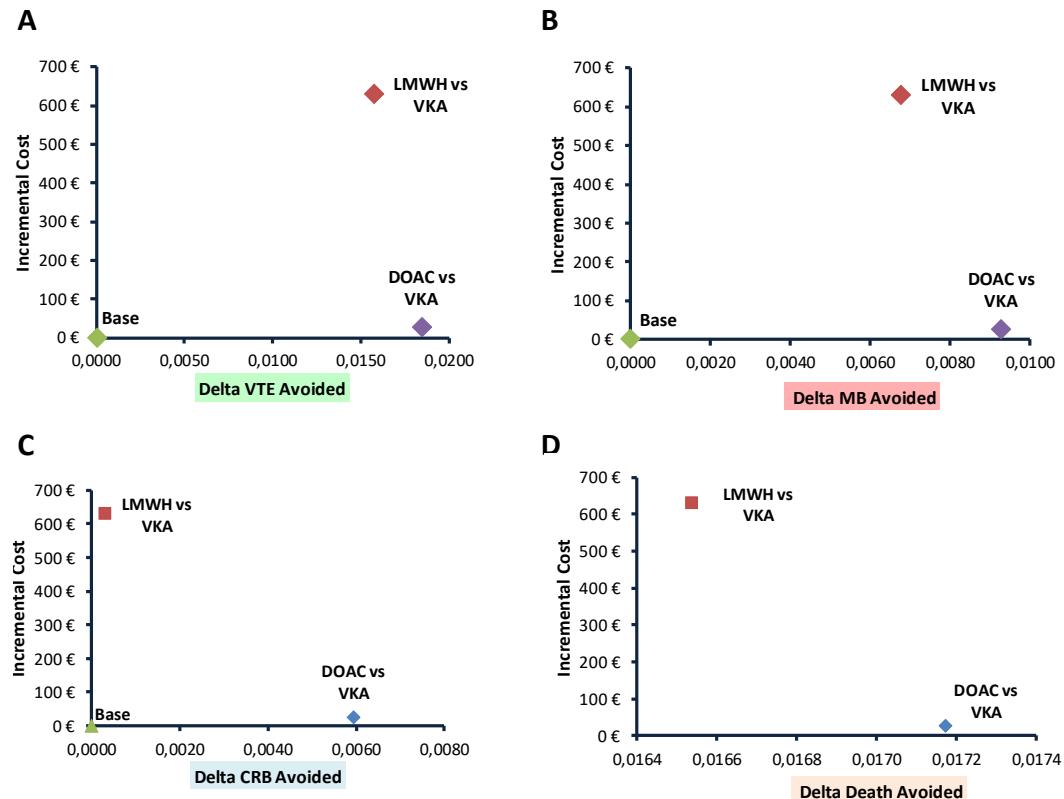


Diagram 6: Cost Effectiveness of different anticoagulation classes (DOAC & LMWH) versus VKA under 6 months treatment in a **Low Risk CAT patient** in different endpoints (A: VTE, B: MB, C: CRB, D: Death)

For the High Risk CAT group, DOAC are characterized with significantly lower ICER value than LMWH for VTE avoidance (nearly €130 compared to €11.200 over VKA base respectively) but with detrimental ICER values for MB and CRB and Death driven by negative safety/efficacy over VKA (Table 12).

This mixed DOAC behavior in the high CAT risk group is based on a negligible increase in total calculated costs vs VKA (nearly +2% or +€8) and their improved VTE profile but significantly worse MB/CRB/Death profile vs VKA.

Comparator	VTE	MB	CRB	Dead	Cost
VKA	10,0%	4,5%	13,7%	41,2%	482 €
DOAC	4,0%	8,8%	22,8%	41,9%	489 €
LMWH	6,1%	5,1%	10,3%	40,9%	907 €

	Δ VTE	Δ MB	Δ CRB	Δ Death	Δ Cost
DOAC vs VKA	5,94%	-4,27%	-9,15%	-0,65%	8 €
LMWH vs VKA	3,80%	-0,58%	12,49%	0,31%	425 €

	ICER VTE Avoided	ICER MB Avoided	ICER CRB Avoided	ICER Death Avoided
DOAC vs VKA	129 €	-179 €	-84 €	-1.173 €
LMWH vs VKA	11.177 €	-73.732 €	3.405 €	137.002 €

*Table 12: Incremental Cost-Effectiveness Analysis of different anticoagulation classes (DOAC & LMWH) versus VKA in a **High Risk CAT patient** under 6 months of anticoagulation (negative figures in red)*

On the other side for the high CAT risk group, LMWH benefits in MB/CRB/Death (except VTE) are significantly better than those of DOAC but are achieved at a considerable increase of the total associated cost over the VKA therapy (+88% or +€425).

LMWH also offer survival gains (associated with higher cost though) resulting at a relative high ICER of more than €100.000 per avoided mortality event (vs VKA as control (table 12 & diagram 7).

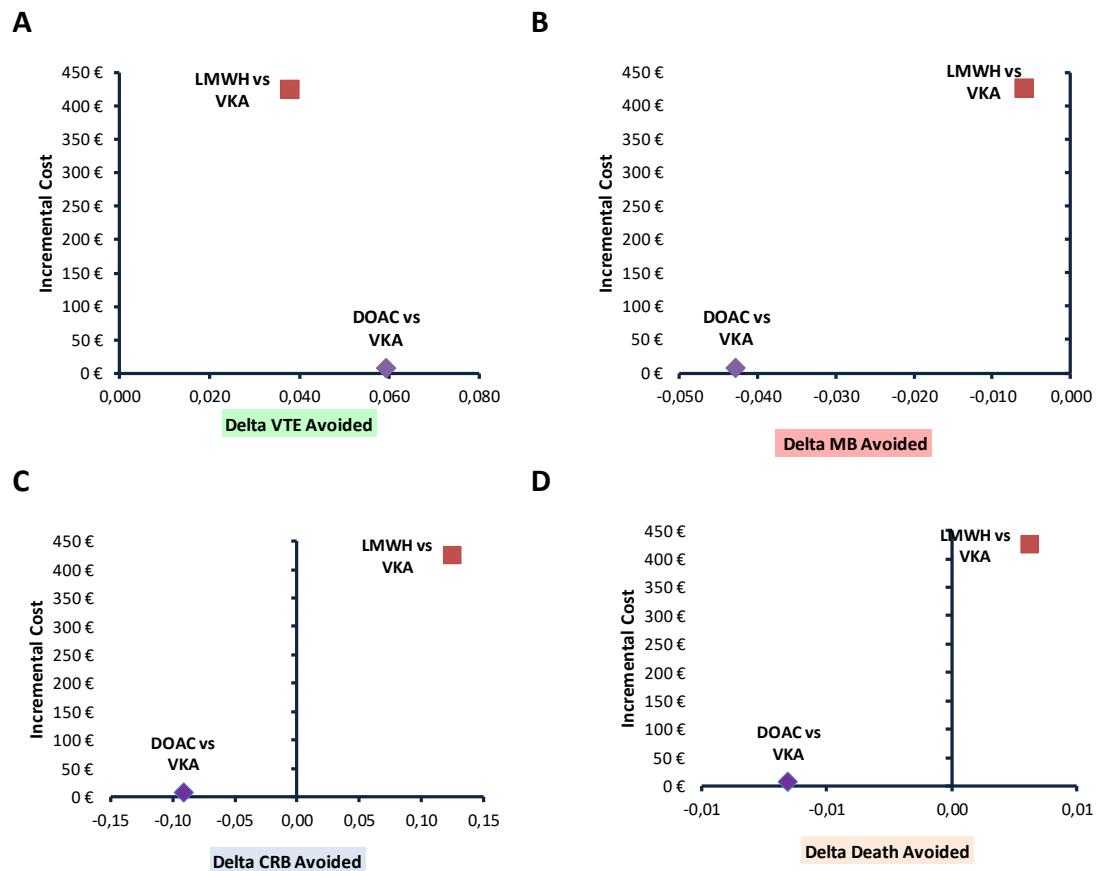


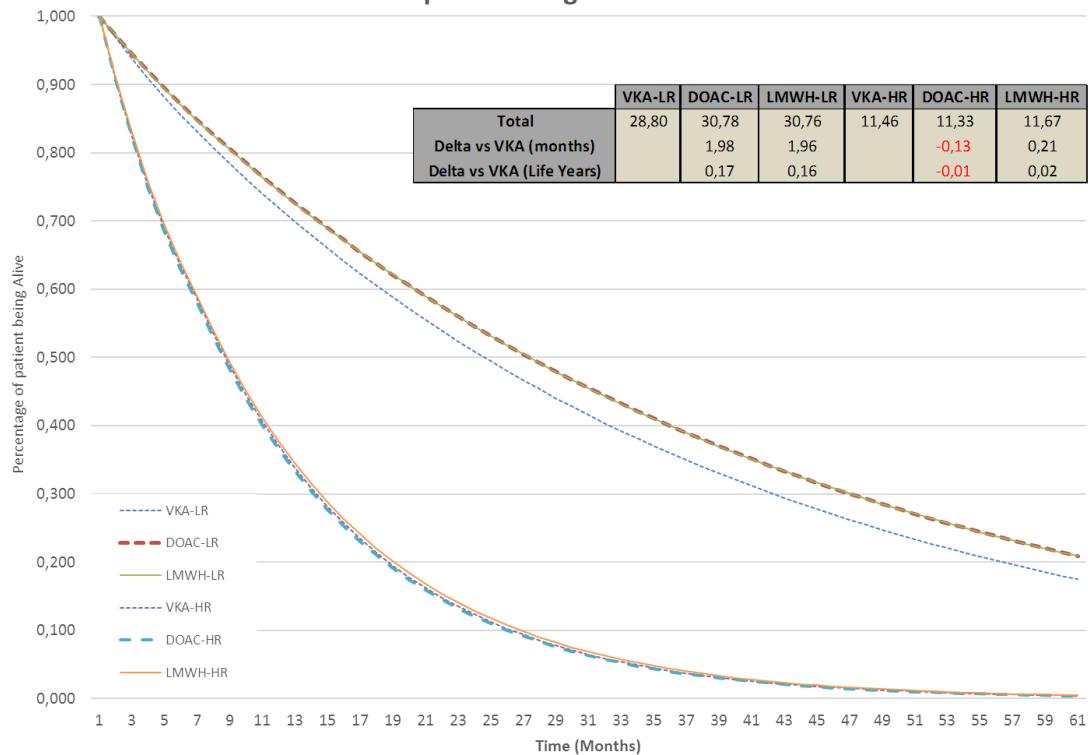
Diagram 7: Cost Effectiveness of different anticoagulation classes (DOAC & LMWH) versus VKA under 6 months treatment in a **High Risk CAT patient** for different endpoints (A: VTE, B: MB, C: CRB, D:Death)

Although the avoided mortality may be a significant cost effectiveness factor, the full extended survival analysis (60 months' timeframe, tables C1, C2 & C3 appendix) and the relative utility based results (tables D1, D2 & D3 appendix) reveal important additional insights for the 2 risk cohorts (diagram 8).

More specifically, for the Low CAT Risk group, survival analysis shows similar LMWH and DOAC benefit over VKA, while in High Risk patients a smaller LMWH benefit and a detrimental DOAC effect over VKA is observed. Similarly to the survival image, the utility analysis reveals benefits of LMWH and DOAC over VKA in the Low CAT risk group and negative DOAC effects in the High Risk Group.

A

Survival Estimation per Anticoagulant choice and Risk Level

**B**

Utility Estimation per Anticoagulant choice and Risk Level

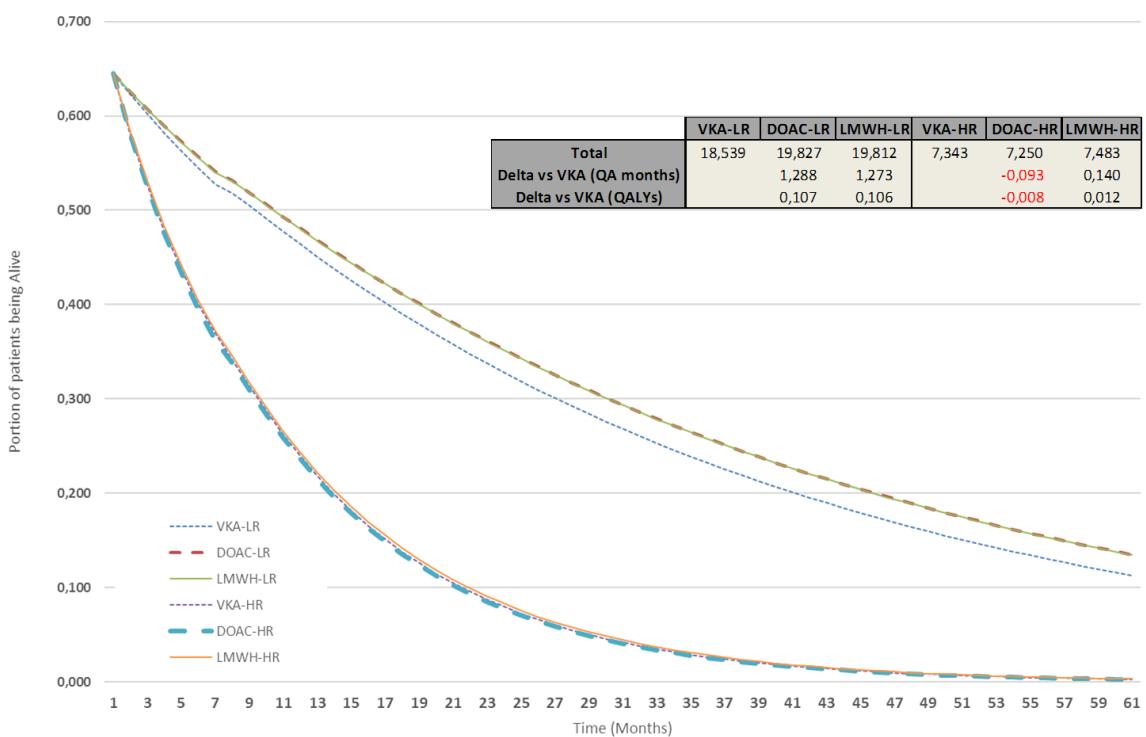


Diagram 8: Long term **Survival (A)** & **Utility (B)** estimations of different anticoagulation classes (VKA, DOAC & LMWH) in **Low Risk (LR)** and **High (HR)** Risk CAT patients

Calculating the relative cost-effectiveness of DOAC in the Low Risk CAT group, a favorable ICER value of less than €300 per LYG or QALY gained (vs VKA base, table 13) is observed which compared with the LMWH ICER of nearly €4.000 per LYG and nearly €6.000 per QALY gained (vs VKA base) is verifying that DOAC are more cost-effective (vs VKA) or even dominant (vs LMWH) in this patient group and therefore a better option than any other class (diagram 9).

Comparator	Low Risk		
	LY	QALY	Cost
VKA	2,400	1,545	437 €
DOAC	2,565	1,652	463 €
LMWH	2,563	1,651	1.066 €
Low Risk			
Comparison	Δ LYG	Δ QALY	ICER LYG
DOAC vs VKA	0,165	0,107	159 €
LMWH vs VKA	0,164	0,106	3.845 €
LMWH vs DOAC	-0,002	-0,001	-343.694 €
			-484.927 €
High Risk			
Comparator	LY	QALY	Cost
VKA	0,955	0,612	482 €
DOAC	0,944	0,604	489 €
LMWH	0,972	0,624	907 €
High Risk			
Comparison	Δ LYG	Δ QALY	ICER LYG
DOAC vs VKA	-0,011	-0,008	-706 €
LMWH vs VKA	0,017	0,012	24.476 €
LMWH vs DOAC	0,028	0,019	14.790 €
			21.539 €

*Table 13: Incremental Cost-Effectiveness & Cost-Utility Analysis of different anticoagulation classes (DOAC & LMWH) versus VKA in a **Low & High Risk CAT patient** under 60 months*

The utility behavior of the DOAC in the High CAT risk group is significantly changed, with negative effects vs VKA as a combined results of mortality and their detrimental MB/CRB contributing profile. DOAC are, in the High CAT Risk group, dominated by the VKA in both LYG and utility aspect, while LMWH offer a high but acceptable ICER of nearly €24.000/LYG and €36.000/QALY gained (vs VKA base), which is also decreasing to nearly €15.000/LYG & €22.000/QALY gained when compared to DOAC as alternative (table 13 & diagram 10).

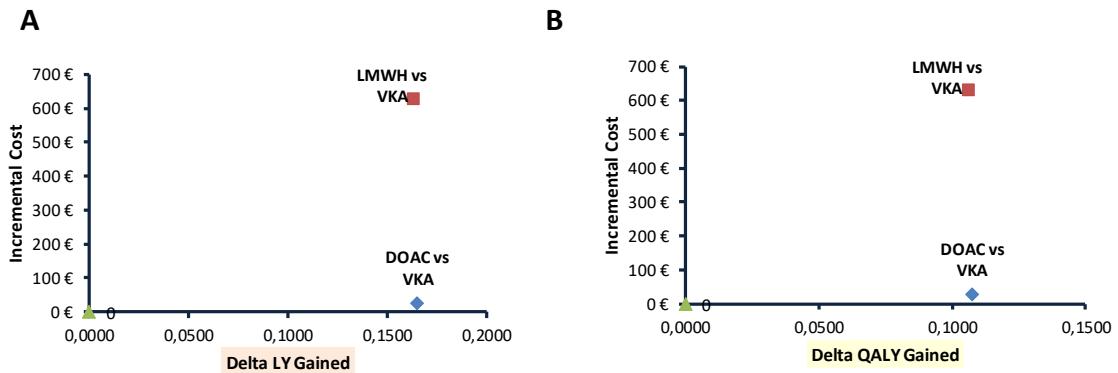


Diagram 9: Cost-Effectiveness in LYG (**A**) and Cost-Utility in QALY (**B**) of different anticoagulation classes (DOAC & LMWH) versus VKA in a **Low Risk CAT patient**

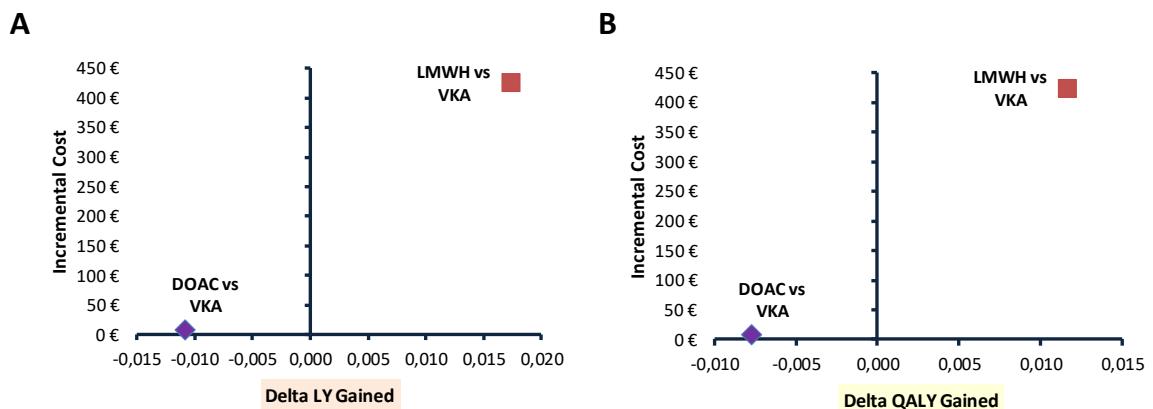


Diagram 10: Cost-Effectiveness in LYG (**A**) and Cost-Utility in QALY (**B**) of different anticoagulation classes (DOAC & LMWH) versus VKA in a **High Risk CAT patient**

4.1 SENSITIVITY ANALYSIS

In the context of the various possibilities for change in costs, a simplified single dimensional sensitivity analysis, accounting various cost possibilities was executed for both Risk CAT levels to evaluate VTE, LYG & QALY ICER changes.

In respect to the possible cost variation of DOAC vs VKA the following events altering the cost of therapies were analyzed:

- a) Future Generic Price Erosion in DOACs (projected at a level of -30% in DOAC average cost)
- b) High Cost Reversal Agents used to handle MB⁴⁰ (+50% in DOAC MB cost)
- c) Unstable INR patients (+80% in VKA costs)
- d) Twice Daily DOAC schedules (projected +30% in DOAC average cost)
- e) Combined total unfavorable DOAC Scenario [case (b)+(d) combined]

Similarly, the analysis of possible cost variation of LMWH vs VKA included the following possible events altering the cost of therapies:

- a) Lower patient weight or cheaper brand choice (projected at a level of -30% LMWH cost of either event)
- b) Future Biosimilar price erosion (projected at a level of -20% in LMWH cost)
- c) Combined favorable price and weight LMWH impacts [case (a)+(b) combined]
- d) Higher weight patient (projected at +30% LMWH dose and cost)
- e) Higher brand price (projected at +20% LMWH cost)
- f) Unstable INR patients (+80% in VKA costs)
- g) Combined total favorable LMWH Scenario [case (c)+(f) combined]

The results of the sensitivity analysis in Low risk CAT patients reveal that DOAC utility ICER may vary between a maximum of nearly €1.300 per QALY gained (total DOAC unfavorable scenario) while a significant cost decrease in their price, or a significant increase of VKA monitoring cost, reclassifies them as dominant solution (table 14).

On the other side LMWH Low Risk sensitivity analysis reveals that pending on weight dosing, cost-utility ratio may increase up to nearly €8.500 per QALY gained while can also decrease considerably in INR instability, which in light of biosimilar

price erosion and lower weight patient might also give significantly favorable cost utility ICER, starting from nearly €1.600 per QALY gained in the total unfavorable VKA scenario (table 14).

In both cases, sensitivity analysis reveals that DOAC remain most probably more cost effective on utility gains when compared with LMWH in the Low risk CAT patient group.

	Event	ICER (VTE Avoided)	ICER LYG	ICER QALY	New Δ Cost
DOAC vs VKA	1. Future Generic Price Erosion in DOACs (-30%)	-4.065 €	-454 €	-699 €	-75 €
	2. High Cost Reversal Agents for MB (50% in MB cost)	2.108 €	235 €	362 €	39 €
	3. Unstable INR patients (+80% in supportive VKA costs)	-8.331 €	-930 €	-1.433 €	-154 €
	4. Twice Daily DOAC schedules (+30% in cost)	6.916 €	772 €	1.189 €	128 €
	5. Total Unfavorable DOAC Scenario (2+4)	7.598 €	848 €	1.307 €	140 €
LMWH vs VKA	1. Lower weight or Cheaper Brand (-30% LMWH dose)	22.154 €	2.132 €	3.288 €	349 €
	2. Future Biosimilar price erosion (-20% in LMWH)	28.083 €	2.703 €	4.168 €	442 €
	3. Combined price and weight (1+2; -45%)	13.259 €	1.276 €	1.968 €	209 €
	4. Higher weight patient (+30% LMWH dose)	57.732 €	5.557 €	8.568 €	909 €
	5. Higher brand price (+20% in LMWH costs)	51.802 €	4.986 €	7.688 €	816 €
	6. Unstable INR patients (+80% in supportive VKA costs)	28.505 €	2.744 €	4.230 €	449 €
	7. Total favorable LMWH Scenario (1+6)	10.715 €	1.031 €	1.590 €	169 €

*Table 14: Single dimensional Sensitivity Analysis of different anticoagulation classes (DOAC & LMWH) versus VKA in a **Low Risk CAT patient** (negative figures in red)*

For the High Risk CAT patients, sensitivity analysis indicates that DOAC incremental cost-utility ICER may become positive in case of a possible lower DOAC price or higher VKA monitoring costs, but this is due to a lower total utility in a lower total cost thus from moving the ICER values from quadrant IV (higher cost/lower utility) to quadrant III (lower cost/lower utility) indicating better VKA cost effectiveness on utility gains (ranging from €9.000-18.000, table 15).

For LMWH and High Risk CAT patients, sensitivity analysis reveals that LMWH drug cost is a significant factor, that in case of 30% increase may elevate the utility ICER at up to nearly €55.000 per QALY gained, while it can nearly halve it (from the base value) to an ICER of nearly €18.000 per QALY gained, when decreased proportionally (-30%, Table 15)

In both cases, sensitivity analysis reveals that LMWH remain most probably more acceptable on utility gains than DOAC in the High risk CAT patient group, as DOAC continued to be dominated or become less cost-effective than VKA.

	Event	ICER (VTE Avoided)	ICER LYG	ICER QALY	New Δ Cost
DOAC vs VKA	1. Future Generic Price Erosion in DOACs (-30%)	-1.156 €	6.319 €	8.889 €	-69 €
	2. Reversal Agents for MB (50% in MB cost)	818 €	-4.474 €	-6.294 €	49 €
	3. Unstable INR patients (+80% in supportive VKA costs)	-2.330 €	12.740 €	17.921 €	-138 €
	4. Twice Daily DOAC schedules (+30% in cost)	1.414 €	-7.731 €	-10.876 €	84 €
	5. Total Unfavorable DOAC Scenario (2+4)	2.103 €	-11.499 €	-16.176 €	125 €
LMWH vs VKA	1. Lower weight or Cheaper Brand (-30% cost)	5.521 €	12.090 €	18.004 €	210 €
	2. Biosimilar price erosion (-20% in LMWH)	7.406 €	16.219 €	24.152 €	282 €
	3. Combined price and weight (1+2; -45%)	2.693 €	5.897 €	8.781 €	102 €
	4. Higher weight patient (+30% LMWH dose)	16.834 €	36.862 €	54.892 €	640 €
	5. Higher brand price (+20% in LMWH costs)	14.948 €	32.733 €	48.744 €	569 €
	6. Unstable INR patients (+80% in supportive VKA costs)	7.339 €	16.072 €	23.933 €	279 €
	7. Total favorable LMWH Scenario (1+6)	1.683 €	3.686 €	5.489 €	64 €

Table 15: Single dimensional Sensitivity Analysis of different anticoagulation classes (DOAC & LMWH) versus VKA in a **High Risk CAT patient** (negative figures in red)

5. DISCUSSION

Use of the optimal long term anticoagulation therapy after VTE establishment remains challenging for cancer patients. LMWH may be more costly in the direct drug cost and add additional burden by the injection inconvenience, nevertheless they represent more efficacious options than VKA and thus the guidelines are supporting them based on their comparative to VKA studies.

LMWH cost effectiveness might be acceptable²¹ but the new DOAC options have arisen, and many health care professionals try to assess their inclusion in the CAT management. Nevertheless, mixed information from DOAC previous trials indicates a probably different class profile in different cancer patients, which newly prospective trials verify with solid efficacy and a more unfavorable (vs LMWH) safety footprint (in terms of MB/CRB) for active cancer (metastasis/chemotherapy) patients.

In the present analysis, and accounting this different thrombotic/bleeding risk of two projected patient groups (High/Low) two major inclusions have been made to analyze with more accuracy the cost effectiveness of those options in CAT; the incorporation of additional mortality risk over the one seen by cancer itself (derived by VTE recurrence as lethal recurrent PE or MB that evolves to be lethal)²³ and the recently published utility values calculated for each of the VTE, MB and CRB states for cancer patients with thrombosis (applicable for all patients under any anticoagulant class).⁷ The utility results, in the context of the Greek healthcare environment, and under these assumptions, indicate that DOAC deem more cost effective in the Low Risk group while LMWH remain acceptably cost effective option for the High Risk group (diagram 11).

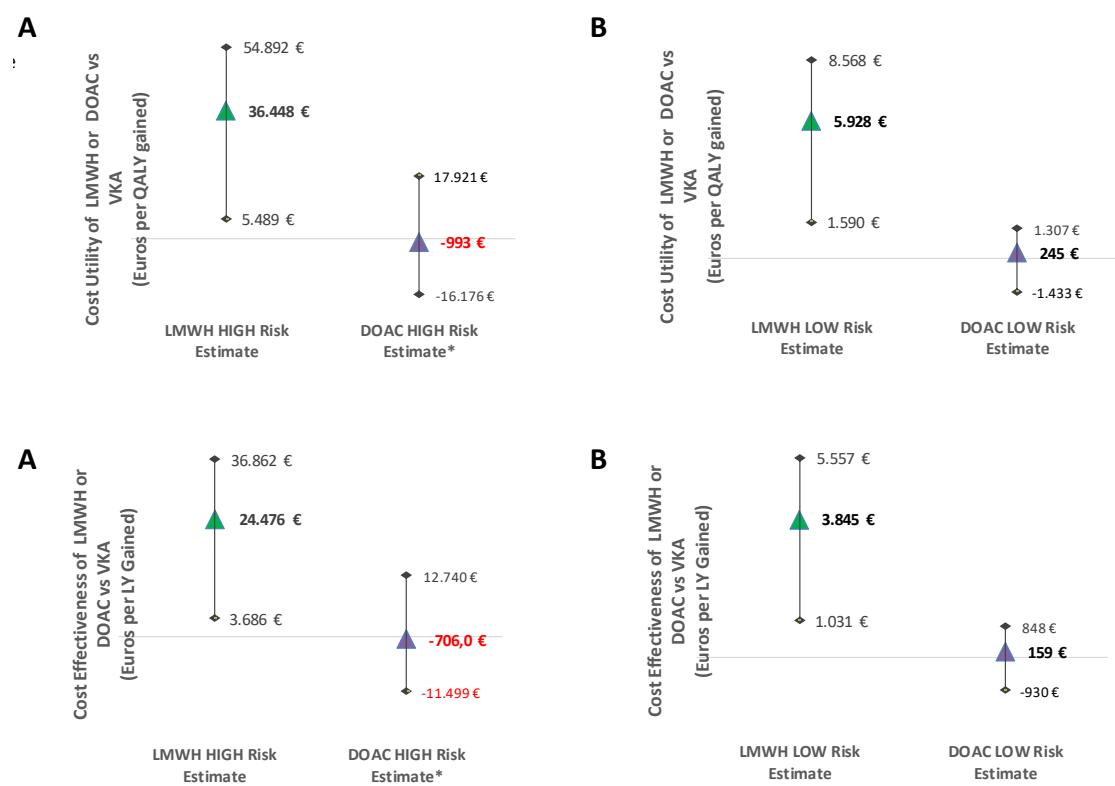
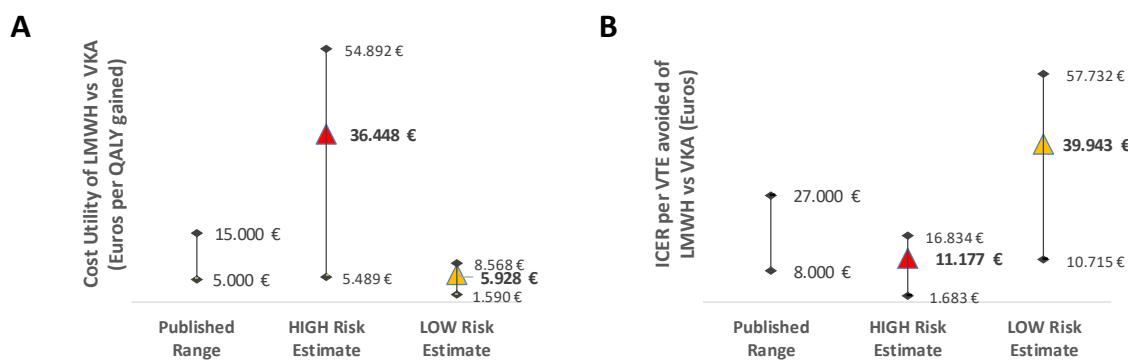


Diagram 11: Estimated ranges of **Cost-Effectiveness (LYG)** and **Cost-Utility (QALY gained)** of LMWH or DOAC vs VKA, incorporating upper and lower limits by sensitivity analysis per **CAT Risk Level (A=High, B=Low)**. *Negative values in High Risk DOAC comparisons are derived by negative LY/QALY changes combined with positive cost benefits and positive values are derived by both negative LY/QALY and cost changes.

The estimated ICER ranges of the LMWH for the High and Low Risk group positively overlap with the range of previously published estimations²¹ and also indicate (under single dimensional sensitivity analysis) that cost-utility might be very sensitive for improvement by the drug price change of each of the different anticoagulant classes (diagram 12).



*Diagram 12: Published²¹ and currently estimated **Cost-Utility** per QALY gained (**A**) or **Cost-Effectiveness** per avoided VTE (**B**) ranges of LMWH versus VKA, incorporating upper and lower limits by sensitivity analysis per CAT Risk Level (High/Low).*

To the best of term paper authors' knowledge, no special pharmaco-economic assessment has been published so far accounting the different cancer patient risks in Greece, but on the other hand the current analysis remains subject to multiple limitations.

A major limitation refers to the design of a simplified assessment model that covers only 6 months of anticoagulation and relative costs, (according trials' evidence), the acceptance of the fact that most of the events (VTE/MB/CRB) occur in the first 6 months period and that the mortality after 6 months would be only altered by cancer disease progression.

The normal, natural age mortality has also not been accounted, nevertheless, as most of the patients had an average age of 50-60 in the trials and with the cancer

mortality leading them to almost full death in the 5 year model, limited changes might be expected.

Additional limitations can also refer to the disease modelling, the calculations of the RR with the indirect methodology (full assumption list; table H appendix), and lack of sensitivity analysis in the RR ratios, nevertheless the scope of the current analysis was not to create an absolute measurement of the cost effectiveness rather than a reliable estimation of probable cost effectiveness differences in various patient risk levels, an outcome that has been clearly different in the 2 patient groups and remained like this under the sensitivity analysis.

6. CONCLUSION

Risk stratification for CAT patients, defined by presence of metastasis and/or use of chemotherapy correlating with higher thrombotic and bleeding risk, might prove useful for achieving higher cost effectiveness from the different anticoagulant classes. According to this clustering and the assumptions of the current analysis in the context of the Greek healthcare environment, DOAC seem a more cost-effective option with favorable utility gains versus standard VKA therapy for the Low Risk CAT patients while LMWH deem more cost effective with acceptable cost-utility gains for High Risk CAT patients.

Single dimensional sensitivity analysis reveals that future cost decrease of DOAC price might further improve their cost effectiveness profile in the Low CAT risk patients but probably might not support them in High CAT risk patients as the utility changes remain negative over VKA, indicating that the positive utility gains of LMWH in this group, might under price sensitivity further improve its acceptable cost utility in the future.

DISCLOSURES/CONFLICT OF INTEREST:

Ioannis Sarigiannidis is an employee of LEO Pharma A/S, which produces and markets LMWH Tinzaparin in Europe and Canada, and has received by LEO unconditional support for his educational development by UPF Barcelona School of management.

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40. Jack E. Ansell, Reversing the Effect of Oral Anticoagulant Drugs: Established and Newer Options, Am J Cardiovasc Drugs 2016, DOI 10.1007/s40256-016-0162-7

APPENDIX

Mortality LR		DOAC LR		VKA LR		MOR DOAC LR		MOR VKA LR		Class Mortality LR			
Study	Comparators	Treatment (days)	Events	n	Events	n	Crude Rate	30d Probability	Weight	Weighted Probability	Comparator	Monthly Probability	Relative Risk**
Prins 2015	Rivaroxaban	VKA	180	38	258	36	0.1473	0.0262	0.5039	0.0132	VKA	0.0284	1.000
Agnelli 2015	Apixaban	VKA	90	5	81	6	0.0617	0.0210	0.1582	0.0033	DOACs	0.0256	0.900
Schulman 2015	Dabigatran	VKA	180	26	173	23	0.1503	0.0268	0.3379	0.0090	LMWH	0.0256	0.900
	Total		69	512	65	444	0.1348	0.0268	1.0000	0.0256	Total	0.0252	1.0000
													0.0284
													Estimated Total Class Probability
													0.0256

VTE LR		DOAC LR		VKA LR		VTE DOAC LR		VTE VKA LR		Class VTE LR			
Study	Comparators	Treatment (days)	Events	n	Events	n	Crude Rate	30d Probability	Weight	Weighted Probability	Comparator	Monthly Probability	Relative Risk*
HOKUSAI 2015	Edoxaban	VKA	180	4	109	7	0.0367	0.0062	0.1755	0.0011	VKA	0.0101	1.000
AMPLIFY	Apixaban	VKA	180	3	81	5	0.0370	0.0063	0.1304	0.0008	DOACs	0.0066	0.650
EINSTEIN DVT+PE	Rivaroxaban	VKA	180	6	258	8	0.0233	0.0039	0.4155	0.0016	LMWH	0.0071	0.700
RECOVER 1+2	Dabigatran	VKA	180	10	173	12	0.0578	0.0099	0.2786	0.0028	%R& Ratios as reported in published Meta-Analysis		
	Total		23	621	32	543	0.0431	0.0127	0.2983	0.0010			
													Estimated Total Class Probability
													0.0101

MB LR		DOAC LR		VKA LR		MB DOAC LR		MB VKA LR		Class MB LR			
Study	Comparators	Treatment (days)	Events	n	Events	n	Crude Rate	30d Probability	Weight	Weighted Probability	Comparator	Monthly Probability	Relative Risk*
HOKUSAI 2015	Edoxaban	VKA	180	5	109	3	0.0459	0.0078	0.1781	0.0014	VKA	0.0010	1.000
AMPLIFY	Apixaban	VKA	180	2	87	4	0.0230	0.0039	0.1422	0.0005	DOACs	0.0050	0.720
EINSTEIN DVT+PE	Rivaroxaban	VKA	180	5	257	8	0.0195	0.0033	0.4199	0.0014	LMWH	0.0055	0.790
RECOVER 1+2	Dabigatran	VKA	180	6	159	7	0.0377	0.0064	0.2598	0.0017	%R& Ratios as reported in published Meta-Analysis		
	Total		18	612	22	533	0.0413	0.0070	0.2852	0.00070			
													Estimated Total Class Probability
													0.0070

CRB LR		DOAC LR		VKA LR		CRB DOAC LR		CRB VKA LR		Class CRB LR			
Study	Comparators	Treatment (days)	Events	n	Events	n	Crude Rate	30d Probability	Weight	Weighted Probability	Comparator	Monthly Probability	Relative Risk*
HOKUSAI 2015	Edoxaban	VKA	180	15	109	22	0.1376	0.0244	0.1857	0.0045	VKA	0.0213	1.000
AMPLIFY	Apixaban	VKA	180	9	87	14	0.1034	0.0180	0.1482	0.0027	DOACs	0.0197	0.923
EINSTEIN DVT+PE	Rivaroxaban	VKA	180	25	232	14	0.1078	0.0188	0.3952	0.0074	LMWH	0.0197	0.923
RECOVER 1+2	Dabigatran	VKA	180	17	159	13	0.1069	0.0187	0.2709	0.0051	%R& Ratios as reported in published Meta-Analysis		
	Total		66	587	63	527	0.1124	0.0200	1.0000	0.0197			
													Estimated Total Class Probability
													0.0197

Table A1 : Relative Risk ratio and Monthly Probabilities calculations of Venous ThromboEmbolism (VTE), Major Bleeding (MB), non-major Clinical Relevant Bleeding (CRB) and Mortality (MOR) based on relative recorded events per DOAC, LMWH and VKA in published comparative trials of LOW CAT RISK patients. Monthly probabilities of VKA calculated based on weighted event (control) rate and DOAC and LMWH monthly Probabilities according meta-analysis risk ratios (*) or calculated ratios from relevant probabilities where not available (**).

** DOAC Risk Ratio calculated via class Probabilities Ratio and LMWH as equal to DOAC

Study	VTE HR			LMWH HR			VKA HR			LMWH HR			VKA HR			Class VTE HR		
	Comparators	Treatment (days)	Events	n	Events	n	Crude Rate	30d Probability	Weight	Crude Rate	30d Probability	Weight	Crude Rate	30d Probability	Weight	Comparator	Monthly Probability	Relative Risk*
CLOT	Dalteparin	VKA	180	27	336	53	0.0804	0.039	0.3191	0.0044	0.1577	0.0282	0.3278	0.0092	VKA	0.0220	1.000	
LITE	Tinzaparin	VKA	90	6	100	10	0.0600	0.0204	0.0950	0.0019	0.0345	0.0034	0.0976	0.0034	LMWH	0.0132	0.600	
Romberg 2009	Tinzaparin	VKA	365	36	33	3	0.0556	0.0347	0.0342	0.0002	0.0909	0.0322	0.0322	0.0003	DOAC	0.0086	0.390	
ONCENDOX	Enoxaparin	VKA	180	4	61	3	0.0656	0.0112	0.0579	0.0007	0.1000	0.0174	0.0293	0.0005				
CATCH	Tinzaparin	VKA	180	31	419	45	0.0690	0.0119	0.4264	0.0051	0.0998	0.0174	0.4400	0.0076				

Study	Comparators	Treatment (days)	MB LMWH HR			MB VKA HR			MB LMWH HR			MB VKA HR		
			Events	n	Events	n	Crude Rate	30d Probability						
CLOT	Dalteparin VKA	180	19	338	12	335	0.0562	0.0096	0.3298	0.0032	0.0358	0.0061	0.3367	0.0020
LITE	Tinzaparin VKA	90	7	100	7	100	0.0700	0.0239	0.0976	0.0023	0.0700	0.0239	0.1005	0.0024
ONCENDOX	Enoxaparin VKA	180	6	67	1	34	0.0896	0.0155	0.0654	0.0029	0.0342	0.0050	0.0342	0.0002
CATCH	Tinzaparin VKA	180	13	419	12	451	0.0290	0.0049	0.0438	0.0010	0.0266	0.0045	0.0453	0.0020
CANTHANOX	Enoxaparin VKA	90	5	71	12	75	0.0704	0.040	0.0693	0.0017	0.1600	0.0565	0.0754	0.0043

Mortality HR		LMWH HR		VKA HR		LMWH HR		VKA HR		Mortality HR	
Study	Comparators	Treatment (days)	Events	n	Events	n	Crude Rate	30d probability	Weight	Crude Rate	30d Probability
CLOT	Dalteparin VKA	180	130	336	136	336	0.3369	0.0783	0.3297	0.4048	0.0828
LITE	Tinzaparin VKA	90	47	100	47	100	0.4700	0.1907	0.0981	0.4700	0.1907
ONCENDOX	Enoxaparin VKA	180	22	67	11	34	0.3784	0.0642	0.0658	0.3735	0.0631
CATCH	Tinzaparin VKA	180	150	449	138	451	0.3341	0.0655	0.4406	0.3060	0.0591
CANTHANOX	Enoxaparin VKA	90	22	67	29	71	0.3284	0.1243	0.0658	0.4085	0.1605
Total	Total	371	1019	361	992	Total	0.3634	0.1243	1.0000	0.3639	0.1112
		Total control	361	992			Estimated Total Class Probability		0.0858	Estimated Total Class Probability	
							Relative Risk *			Relative Risk *	
							VKA	0.0878		LMWH	0.0858
							DOAC	0.0884		DOAC	0.0884

* LMWH/Risk Ratio calculated via Class Probabilities Ratio and DOAC via indirect network calculation

Table A2: Relative Risk ratios and Monthly Probabilities calculations of Venous ThromboEmbolism (VTE), Major Bleeding (MB), non-major Clinical Relevant Bleeding (CRB) and Mortality (MOR) based on relative recorded events per DOAC, LMWH and VKA in published comparative trials of HIGH CAT RISK patients. Monthly probabilities of VKA calculated based on weighted event (control) rates with exponential distribution and DOAC and LMWH monthly probabilities according meta-analysis risk ratios vs VKA probabilities (*) or calculated as ratios from relevant probabilities where not available (**).

VKA		Destination				Destination			
Low Risk Cohort		Thrombo-Px	MB	VTE	CRB	Thrombo-Px	MB	VTE	CRB
Origin	Thrombo-Px	0,9298	0,0070	0,0101	0,0213	0,8411	0,0109	0,0220	0,0320
	MB	0,9899	0,0101	1,0000	0,0318	0,9780	0,0220	1,0000	0,0940
	VTE	0,0101	1,0000	0,0318	0,0940	0,0109	0,0220	1,0000	1,0000
	CRB	0,0101	0,0318	0,0940	1,0000	0,8731	0,0109	0,0220	1,0000
	Death	1,0000	1,0000	1,0000	1,0000				

DOAC		Destination				Destination			
Low Risk Cohort		Thrombo-Px	MB	VTE	CRB	Thrombo-Px	MB	VTE	CRB
Origin	Thrombo-Px	0,9408	0,0050	0,0066	0,0197	0,8224	0,0203	0,0086	0,0541
	MB	0,9934	0,0066	1,0000	0,0279	0,9914	0,0086	1,0000	0,0947
	VTE	0,0050	1,0000	0,0066	0,0279	0,8764	0,0203	0,0086	0,0947
	CRB	0,9605	0,0050	0,0066	0,0279				1,0000
	Death	1,0000	1,0000	1,0000	1,0000				

LMWH		Destination				Destination			
Low Risk Cohort		Thrombo-Px	MB	VTE	CRB	Thrombo-Px	MB	VTE	CRB
Origin	Thrombo-Px	0,9396	0,0055	0,0071	0,0197	0,8610	0,0117	0,0132	0,0234
	MB	0,9929	0,0071	1,0000	0,0281	0,9888	0,0132	1,0000	0,0908
	VTE	0,0055	0,0071	0,0281	1,0000	0,8844	0,0117	0,0132	1,0000
	CRB	0,9593	0,0055	0,0281	1,0000				1,0000
	Death	1,0000	1,0000	1,0000	1,0000				

Table B1: Stage 1 monthly transition probabilities matrix between model states under different anticoagulant classes (VKA, DOAC & LMWH) in Low and High Risk CAT patient cohort ($n=1,00$)

VKA		Destination					Check	
		High Risk Cohort	Thrombo-Px	MB	VTE	CRB		
Low Risk Cohort		0,9716	0,3000	0,3000	0,3000	0,3000	0,0284	1,0000
Thrombo-Px	MB	0,6716	0,6716	0,6716	0,6716	0,6716	0,0284	1,0000
Origin	VTE	CRB	Death				0,0284	1,0000
							0,0284	1,0000
DOAC		Destination					Check	
		High Risk Cohort	Thrombo-Px	MB	VTE	CRB		
Low Risk Cohort		0,9744	0,3000	0,3000	0,3000	0,3000	0,0256	1,0000
Thrombo-Px	MB	0,6744	0,6744	0,6744	0,6744	0,6744	0,0256	1,0000
Origin	VTE	CRB	Death				0,0256	1,0000
							0,0256	1,0000
LMWH		Destination					Check	
		High Risk Cohort	Thrombo-Px	MB	VTE	CRB		
Low Risk Cohort		0,9744	0,3000	0,3000	0,3000	0,3000	0,0256	1,0000
Thrombo-Px	MB	0,6744	0,6744	0,6744	0,6744	0,6744	0,0256	1,0000
Origin	VTE	CRB	Death				0,0256	1,0000
							0,0256	1,0000

Table B2: Stage 2 Monthly transition probabilities matrix between model states (6-60 months) under different anticoagulant classes (VKA, DOAC & LMWH) in Low and High Risk CAT patient cohort ($n=1,000$)

VKA	Low Risk Cohort					Check	VKA	High Risk Cohort					Check
Month	Thrombo-Px	MB	VTE	CRB	Dead		Month	Thrombo-Px	MB	VTE	CRB	Dead	
0	1,0000	0,0000	0,0000	0,0000	0,0000	1,0000	0	1,0000	0,0000	0,0000	0,0000	0,0000	1,0000
1	0,9298	0,0070	0,0101	0,0213	0,0318	1,0000	1	0,8411	0,0109	0,0220	0,0320	0,0940	1,0000
2	0,8848	0,0136	0,0198	0,0198	0,0620	1,0000	2	0,7354	0,0202	0,0415	0,0270	0,1760	1,0000
3	0,8416	0,0198	0,0290	0,0189	0,0907	1,0000	3	0,6421	0,0280	0,0587	0,0236	0,2477	1,0000
4	0,8004	0,0256	0,0379	0,0179	0,1181	1,0000	4	0,5606	0,0347	0,0739	0,0206	0,3102	1,0000
5	0,7613	0,0311	0,0464	0,0171	0,1441	1,0000	5	0,4895	0,0403	0,0875	0,0180	0,3648	1,0000
6	0,7241	0,0362	0,0546	0,0162	0,1688	1,0000	6	0,4274	0,0449	0,0995	0,0157	0,4125	1,0000
7	0,7754	0,0109	0,0164	0,0049	0,1925	1,0000	7	0,4879	0,0135	0,0299	0,0047	0,4641	1,0000
8	0,7749	0,0033	0,0049	0,0015	0,2154	1,0000	8	0,4745	0,0040	0,0090	0,0014	0,5111	1,0000
9	0,7594	0,0010	0,0015	0,0004	0,2377	1,0000	9	0,4416	0,0012	0,0027	0,0004	0,5540	1,0000
10	0,7397	0,0003	0,0004	0,0001	0,2594	1,0000	10	0,4055	0,0004	0,0008	0,0001	0,5932	1,0000
11	0,7192	0,0001	0,0001	0,0000	0,2805	1,0000	11	0,3707	0,0001	0,0002	0,0000	0,6289	1,0000
12	0,6990	0,0000	0,0000	0,0000	0,3010	1,0000	12	0,3384	0,0000	0,0001	0,0000	0,6615	1,0000
13	0,6791	0,0000	0,0000	0,0000	0,3209	1,0000	13	0,3088	0,0000	0,0000	0,0000	0,6912	1,0000
14	0,6598	0,0000	0,0000	0,0000	0,3402	1,0000	14	0,2817	0,0000	0,0000	0,0000	0,7183	1,0000
15	0,6410	0,0000	0,0000	0,0000	0,3590	1,0000	15	0,2570	0,0000	0,0000	0,0000	0,7430	1,0000
16	0,6228	0,0000	0,0000	0,0000	0,3772	1,0000	16	0,2344	0,0000	0,0000	0,0000	0,7656	1,0000
17	0,6051	0,0000	0,0000	0,0000	0,3949	1,0000	17	0,2138	0,0000	0,0000	0,0000	0,7862	1,0000
18	0,5879	0,0000	0,0000	0,0000	0,4121	1,0000	18	0,1951	0,0000	0,0000	0,0000	0,8049	1,0000
19	0,5712	0,0000	0,0000	0,0000	0,4288	1,0000	19	0,1779	0,0000	0,0000	0,0000	0,8221	1,0000
20	0,5549	0,0000	0,0000	0,0000	0,4451	1,0000	20	0,1623	0,0000	0,0000	0,0000	0,8377	1,0000
21	0,5391	0,0000	0,0000	0,0000	0,4609	1,0000	21	0,1481	0,0000	0,0000	0,0000	0,8519	1,0000
22	0,5238	0,0000	0,0000	0,0000	0,4762	1,0000	22	0,1351	0,0000	0,0000	0,0000	0,8649	1,0000
23	0,5089	0,0000	0,0000	0,0000	0,4911	1,0000	23	0,1232	0,0000	0,0000	0,0000	0,8768	1,0000
24	0,4944	0,0000	0,0000	0,0000	0,5056	1,0000	24	0,1124	0,0000	0,0000	0,0000	0,8876	1,0000
25	0,4803	0,0000	0,0000	0,0000	0,5197	1,0000	25	0,1025	0,0000	0,0000	0,0000	0,8975	1,0000
26	0,4667	0,0000	0,0000	0,0000	0,5333	1,0000	26	0,0935	0,0000	0,0000	0,0000	0,9065	1,0000
27	0,4534	0,0000	0,0000	0,0000	0,5466	1,0000	27	0,0853	0,0000	0,0000	0,0000	0,9147	1,0000
28	0,4405	0,0000	0,0000	0,0000	0,5595	1,0000	28	0,0778	0,0000	0,0000	0,0000	0,9222	1,0000
29	0,4280	0,0000	0,0000	0,0000	0,5720	1,0000	29	0,0710	0,0000	0,0000	0,0000	0,9290	1,0000
30	0,4158	0,0000	0,0000	0,0000	0,5842	1,0000	30	0,0648	0,0000	0,0000	0,0000	0,9352	1,0000
31	0,4040	0,0000	0,0000	0,0000	0,5960	1,0000	31	0,0591	0,0000	0,0000	0,0000	0,9409	1,0000
32	0,3925	0,0000	0,0000	0,0000	0,6075	1,0000	32	0,0539	0,0000	0,0000	0,0000	0,9461	1,0000
33	0,3813	0,0000	0,0000	0,0000	0,6187	1,0000	33	0,0492	0,0000	0,0000	0,0000	0,9508	1,0000
34	0,3705	0,0000	0,0000	0,0000	0,6295	1,0000	34	0,0448	0,0000	0,0000	0,0000	0,9552	1,0000
35	0,3599	0,0000	0,0000	0,0000	0,6401	1,0000	35	0,0409	0,0000	0,0000	0,0000	0,9591	1,0000
36	0,3497	0,0000	0,0000	0,0000	0,6503	1,0000	36	0,0373	0,0000	0,0000	0,0000	0,9627	1,0000
37	0,3397	0,0000	0,0000	0,0000	0,6603	1,0000	37	0,0340	0,0000	0,0000	0,0000	0,9660	1,0000
38	0,3301	0,0000	0,0000	0,0000	0,6699	1,0000	38	0,0311	0,0000	0,0000	0,0000	0,9689	1,0000
39	0,3207	0,0000	0,0000	0,0000	0,6793	1,0000	39	0,0283	0,0000	0,0000	0,0000	0,9717	1,0000
40	0,3116	0,0000	0,0000	0,0000	0,6884	1,0000	40	0,0258	0,0000	0,0000	0,0000	0,9742	1,0000
41	0,3027	0,0000	0,0000	0,0000	0,6973	1,0000	41	0,0236	0,0000	0,0000	0,0000	0,9764	1,0000
42	0,2941	0,0000	0,0000	0,0000	0,7059	1,0000	42	0,0215	0,0000	0,0000	0,0000	0,9785	1,0000
43	0,2857	0,0000	0,0000	0,0000	0,7143	1,0000	43	0,0196	0,0000	0,0000	0,0000	0,9804	1,0000
44	0,2776	0,0000	0,0000	0,0000	0,7224	1,0000	44	0,0179	0,0000	0,0000	0,0000	0,9821	1,0000
45	0,2697	0,0000	0,0000	0,0000	0,7303	1,0000	45	0,0163	0,0000	0,0000	0,0000	0,9837	1,0000
46	0,2620	0,0000	0,0000	0,0000	0,7380	1,0000	46	0,0149	0,0000	0,0000	0,0000	0,9851	1,0000
47	0,2546	0,0000	0,0000	0,0000	0,7454	1,0000	47	0,0136	0,0000	0,0000	0,0000	0,9864	1,0000
48	0,2473	0,0000	0,0000	0,0000	0,7527	1,0000	48	0,0124	0,0000	0,0000	0,0000	0,9876	1,0000
49	0,2403	0,0000	0,0000	0,0000	0,7597	1,0000	49	0,0113	0,0000	0,0000	0,0000	0,9887	1,0000
50	0,2334	0,0000	0,0000	0,0000	0,7666	1,0000	50	0,0103	0,0000	0,0000	0,0000	0,9897	1,0000
51	0,2268	0,0000	0,0000	0,0000	0,7732	1,0000	51	0,0094	0,0000	0,0000	0,0000	0,9906	1,0000
52	0,2204	0,0000	0,0000	0,0000	0,7796	1,0000	52	0,0086	0,0000	0,0000	0,0000	0,9914	1,0000
53	0,2141	0,0000	0,0000	0,0000	0,7859	1,0000	53	0,0078	0,0000	0,0000	0,0000	0,9922	1,0000
54	0,2080	0,0000	0,0000	0,0000	0,7920	1,0000	54	0,0071	0,0000	0,0000	0,0000	0,9929	1,0000
55	0,2021	0,0000	0,0000	0,0000	0,7979	1,0000	55	0,0065	0,0000	0,0000	0,0000	0,9935	1,0000
56	0,1963	0,0000	0,0000	0,0000	0,8037	1,0000	56	0,0059	0,0000	0,0000	0,0000	0,9941	1,0000
57	0,1907	0,0000	0,0000	0,0000	0,8093	1,0000	57	0,0054	0,0000	0,0000	0,0000	0,9946	1,0000
58	0,1853	0,0000	0,0000	0,0000	0,8147	1,0000	58	0,0049	0,0000	0,0000	0,0000	0,9951	1,0000
59	0,1800	0,0000	0,0000	0,0000	0,8200	1,0000	59	0,0045	0,0000	0,0000	0,0000	0,9955	1,0000
60	0,1749	0,0000	0,0000	0,0000	0,8251	1,0000	60	0,0041	0,0000	0,0000	0,0000	0,9959	1,0000

Table C1: 6-month (stage1) and 60-month (stage2*) Markov model event estimations for **VKA treatment** in Low and High Risk CAT patient cohort ($n=1,000$)

*"Thrombo-Px" state is not exposed to any anticoagulants nor costs from month 7 onwards and represents the alive event free patients

DOAC						Low Risk Cohort						DOAC						High Risk Cohort					
Month	Thrombo-Px	MB	VTE	CRB	Dead	Check	Month	Thrombo-Px	MB	VTE	CRB	Dead	Check	Month	Thrombo-Px	MB	VTE	CRB	Dead	Check			
0	1,0000	0,0000	0,0000	0,0000	0,0000	1,0000	0	1,0000	0,0000	0,0000	0,0000	0,0000	1,0000	0	1,0000	0,0000	0,0000	0,0000	0,0000	1,0000			
1	0,9408	0,0050	0,0066	0,0197	0,0279	1,0000	1	0,8224	0,0203	0,0086	0,0541	0,0947	1,0000	2	0,7237	0,0379	0,0163	0,0445	0,1777	1,0000			
2	0,9041	0,0099	0,0129	0,0185	0,0547	1,0000	3	0,6341	0,0532	0,0232	0,0391	0,2504	1,0000	4	0,5557	0,0664	0,0294	0,0343	0,3142	1,0000			
3	0,8684	0,0144	0,0190	0,0178	0,0804	1,0000	5	0,8011	0,0230	0,0306	0,0164	0,1288	1,0000	6	0,7695	0,0270	0,0361	0,0158	0,1516	1,0000			
7	0,8030	0,0081	0,0108	0,0047	0,1734	1,0000	7	0,4834	0,0263	0,0120	0,0079	0,4704	1,0000	8	0,7984	0,0024	0,0033	0,0014	0,1945	1,0000			
8	0,7984	0,0024	0,0033	0,0014	0,1945	1,0000	9	0,7827	0,0007	0,0010	0,0004	0,2151	1,0000	10	0,7641	0,0002	0,0003	0,0001	0,2352	1,0000			
11	0,7450	0,0001	0,0001	0,0000	0,2548	1,0000	12	0,7260	0,0000	0,0000	0,0000	0,2739	1,0000	13	0,7075	0,0000	0,0000	0,0000	0,2925	1,0000			
14	0,6894	0,0000	0,0000	0,0000	0,3106	1,0000	15	0,6717	0,0000	0,0000	0,0000	0,3283	1,0000	16	0,6545	0,0000	0,0000	0,0000	0,3455	1,0000			
17	0,6378	0,0000	0,0000	0,0000	0,3622	1,0000	18	0,6215	0,0000	0,0000	0,0000	0,3785	1,0000	19	0,6055	0,0000	0,0000	0,0000	0,3945	1,0000			
20	0,5900	0,0000	0,0000	0,0000	0,4100	1,0000	21	0,5749	0,0000	0,0000	0,0000	0,4251	1,0000	22	0,5602	0,0000	0,0000	0,0000	0,4398	1,0000			
23	0,5459	0,0000	0,0000	0,0000	0,4541	1,0000	24	0,5319	0,0000	0,0000	0,0000	0,4681	1,0000	25	0,5183	0,0000	0,0000	0,0000	0,4817	1,0000			
26	0,5050	0,0000	0,0000	0,0000	0,4950	1,0000	27	0,4921	0,0000	0,0000	0,0000	0,5079	1,0000	28	0,4795	0,0000	0,0000	0,0000	0,5205	1,0000			
29	0,4672	0,0000	0,0000	0,0000	0,5328	1,0000	30	0,4552	0,0000	0,0000	0,0000	0,5448	1,0000	31	0,4436	0,0000	0,0000	0,0000	0,5564	1,0000			
32	0,4322	0,0000	0,0000	0,0000	0,5678	1,0000	33	0,4212	0,0000	0,0000	0,0000	0,5788	1,0000	34	0,4104	0,0000	0,0000	0,0000	0,5896	1,0000			
35	0,3999	0,0000	0,0000	0,0000	0,6001	1,0000	36	0,3896	0,0000	0,0000	0,0000	0,6104	1,0000	37	0,3796	0,0000	0,0000	0,0000	0,6204	1,0000			
38	0,3699	0,0000	0,0000	0,0000	0,6301	1,0000	39	0,3605	0,0000	0,0000	0,0000	0,6395	1,0000	40	0,3512	0,0000	0,0000	0,0000	0,6488	1,0000			
41	0,3422	0,0000	0,0000	0,0000	0,6578	1,0000	42	0,3335	0,0000	0,0000	0,0000	0,6665	1,0000	43	0,3249	0,0000	0,0000	0,0000	0,6751	1,0000			
44	0,3166	0,0000	0,0000	0,0000	0,6834	1,0000	45	0,3085	0,0000	0,0000	0,0000	0,6915	1,0000	46	0,3006	0,0000	0,0000	0,0000	0,6994	1,0000			
47	0,2929	0,0000	0,0000	0,0000	0,7071	1,0000	48	0,2854	0,0000	0,0000	0,0000	0,7146	1,0000	49	0,2781	0,0000	0,0000	0,0000	0,7219	1,0000			
50	0,2710	0,0000	0,0000	0,0000	0,7290	1,0000	51	0,2640	0,0000	0,0000	0,0000	0,7360	1,0000	52	0,2573	0,0000	0,0000	0,0000	0,7427	1,0000			
53	0,2507	0,0000	0,0000	0,0000	0,7493	1,0000	54	0,2443	0,0000	0,0000	0,0000	0,7557	1,0000	55	0,2380	0,0000	0,0000	0,0000	0,7620	1,0000			
56	0,2319	0,0000	0,0000	0,0000	0,7681	1,0000	57	0,2260	0,0000	0,0000	0,0000	0,7740	1,0000	58	0,2202	0,0000	0,0000	0,0000	0,7798	1,0000			
59	0,2146	0,0000	0,0000	0,0000	0,7854	1,0000	60	0,2091	0,0000	0,0000	0,0000	0,7909	1,0000										

Table C2: 6-month (stage1) and 60-month (stage2*) Markov model event estimations for DOAC treatment in Low and High Risk CAT patient cohort (n=1,000)

*"Thrombo-Px" state is not exposed to any anticoagulants nor costs from month 7 onwards and represents the alive event free patients

LMWH	Low Risk Cohort					Check	
	Month	Thrombo-Px	MB	VTE	CRB	Dead	
0	1,0000	0,0000	0,0000	0,0000	0,0000	0,0000	1,0000
1	0,9396	0,0055	0,0071	0,0197	0,0281	0,0000	1,0000
2	0,9018	0,0108	0,0139	0,0185	0,0550	0,0000	1,0000
3	0,8651	0,0158	0,0205	0,0178	0,0809	0,0000	1,0000
4	0,8299	0,0206	0,0268	0,0170	0,1057	0,0000	1,0000
5	0,7961	0,0251	0,0329	0,0163	0,1295	0,0000	1,0000
6	0,7637	0,0294	0,0388	0,0157	0,1523	0,0000	1,0000
7	0,8008	0,0088	0,0117	0,0047	0,1740	0,0000	1,0000
8	0,7973	0,0027	0,0035	0,0014	0,1951	0,0000	1,0000
9	0,7820	0,0008	0,0010	0,0004	0,2157	0,0000	1,0000
10	0,7635	0,0002	0,0003	0,0001	0,2358	0,0000	1,0000
11	0,7444	0,0001	0,0001	0,0000	0,2554	0,0000	1,0000
12	0,7255	0,0000	0,0000	0,0000	0,2744	0,0000	1,0000
13	0,7070	0,0000	0,0000	0,0000	0,2930	0,0000	1,0000
14	0,6889	0,0000	0,0000	0,0000	0,3111	0,0000	1,0000
15	0,6712	0,0000	0,0000	0,0000	0,3288	0,0000	1,0000
16	0,6541	0,0000	0,0000	0,0000	0,3459	0,0000	1,0000
17	0,6373	0,0000	0,0000	0,0000	0,3627	0,0000	1,0000
18	0,6210	0,0000	0,0000	0,0000	0,3790	0,0000	1,0000
19	0,6051	0,0000	0,0000	0,0000	0,3949	0,0000	1,0000
20	0,5896	0,0000	0,0000	0,0000	0,4104	0,0000	1,0000
21	0,5745	0,0000	0,0000	0,0000	0,4255	0,0000	1,0000
22	0,5598	0,0000	0,0000	0,0000	0,4402	0,0000	1,0000
23	0,5455	0,0000	0,0000	0,0000	0,4545	0,0000	1,0000
24	0,5315	0,0000	0,0000	0,0000	0,4685	0,0000	1,0000
25	0,5179	0,0000	0,0000	0,0000	0,4821	0,0000	1,0000
26	0,5046	0,0000	0,0000	0,0000	0,4954	0,0000	1,0000
27	0,4917	0,0000	0,0000	0,0000	0,5083	0,0000	1,0000
28	0,4791	0,0000	0,0000	0,0000	0,5209	0,0000	1,0000
29	0,4668	0,0000	0,0000	0,0000	0,5332	0,0000	1,0000
30	0,4549	0,0000	0,0000	0,0000	0,5451	0,0000	1,0000
31	0,4432	0,0000	0,0000	0,0000	0,5568	0,0000	1,0000
32	0,4319	0,0000	0,0000	0,0000	0,5681	0,0000	1,0000
33	0,4208	0,0000	0,0000	0,0000	0,5792	0,0000	1,0000
34	0,4101	0,0000	0,0000	0,0000	0,5899	0,0000	1,0000
35	0,3996	0,0000	0,0000	0,0000	0,6004	0,0000	1,0000
36	0,3893	0,0000	0,0000	0,0000	0,6107	0,0000	1,0000
37	0,3794	0,0000	0,0000	0,0000	0,6206	0,0000	1,0000
38	0,3697	0,0000	0,0000	0,0000	0,6303	0,0000	1,0000
39	0,3602	0,0000	0,0000	0,0000	0,6398	0,0000	1,0000
40	0,3510	0,0000	0,0000	0,0000	0,6490	0,0000	1,0000
41	0,3420	0,0000	0,0000	0,0000	0,6580	0,0000	1,0000
42	0,3332	0,0000	0,0000	0,0000	0,6668	0,0000	1,0000
43	0,3247	0,0000	0,0000	0,0000	0,6753	0,0000	1,0000
44	0,3164	0,0000	0,0000	0,0000	0,6836	0,0000	1,0000
45	0,3083	0,0000	0,0000	0,0000	0,6917	0,0000	1,0000
46	0,3004	0,0000	0,0000	0,0000	0,6996	0,0000	1,0000
47	0,2927	0,0000	0,0000	0,0000	0,7073	0,0000	1,0000
48	0,2852	0,0000	0,0000	0,0000	0,7148	0,0000	1,0000
49	0,2779	0,0000	0,0000	0,0000	0,7221	0,0000	1,0000
50	0,2708	0,0000	0,0000	0,0000	0,7292	0,0000	1,0000
51	0,2638	0,0000	0,0000	0,0000	0,7362	0,0000	1,0000
52	0,2571	0,0000	0,0000	0,0000	0,7429	0,0000	1,0000
53	0,2505	0,0000	0,0000	0,0000	0,7495	0,0000	1,0000
54	0,2441	0,0000	0,0000	0,0000	0,7559	0,0000	1,0000
55	0,2378	0,0000	0,0000	0,0000	0,7622	0,0000	1,0000
56	0,2318	0,0000	0,0000	0,0000	0,7682	0,0000	1,0000
57	0,2258	0,0000	0,0000	0,0000	0,7742	0,0000	1,0000
58	0,2200	0,0000	0,0000	0,0000	0,7800	0,0000	1,0000
59	0,2144	0,0000	0,0000	0,0000	0,7856	0,0000	1,0000
60	0,2089	0,0000	0,0000	0,0000	0,7911	0,0000	1,0000

LMWH	High Risk Cohort					Check
	Month	Thrombo-Px	MB	VTE	CRB	
0	1,0000	0,0000	0,0000	0,0000	0,0000	0,0000
1	0,8610	0,0117	0,0132	0,0234	0,0908	0,0000
2	0,7620	0,0218	0,0250	0,0202	0,1710	0,0000
3	0,6739	0,0307	0,0356	0,0178	0,2420	0,0000
4	0,5959	0,0383	0,0452	0,0158	0,3048	0,0000
5	0,5270	0,0450	0,0538	0,0139	0,3603	0,0000
6	0,4661	0,0507	0,0615	0,0123	0,4094	0,0000
7	0,5026	0,0152	0,0184	0,0037	0,4601	0,0000
8	0,4824	0,0046	0,0055	0,0011	0,5064	0,0000
9	0,4479	0,0014	0,0017	0,0003	0,5487	0,0000
10	0,4115	0,0004	0,0005	0,0001	0,5875	0,0000
11	0,3768	0,0001	0,0000	0,0000	0,6228	0,0000
12	0,3447	0,0000	0,0000	0,0000	0,6552	0,0000
13	0,3152	0,0000	0,0000	0,0000	0,6848	0,0000
14	0,2882	0,0000	0,0000	0,0000	0,7118	0,0000
15	0,2634	0,0000	0,0000	0,0000	0,7366	0,0000
16	0,2408	0,0000	0,0000	0,0000	0,7592	0,0000
17	0,2202	0,0000	0,0000	0,0000	0,7798	0,0000
18	0,2013	0,0000	0,0000	0,0000	0,7987	0,0000
19	0,1840	0,0000	0,0000	0,0000	0,8160	0,0000
20	0,1682	0,0000	0,0000	0,0000	0,8318	0,0000
21	0,1538	0,0000	0,0000	0,0000	0,8462	0,0000
22	0,1406	0,0000	0,0000	0,0000	0,8594	0,0000
23	0,1285	0,0000	0,0000	0,0000	0,8715	0,0000
24	0,1175	0,0000	0,0000	0,0000	0,8825	0,0000
25	0,1074	0,0000	0,0000	0,0000	0,8926	0,0000
26	0,0982	0,0000	0,0000	0,0000	0,9018	0,0000
27	0,0898	0,0000	0,0000	0,0000	0,9102	0,0000
28	0,0821	0,0000	0,0000	0,0000	0,9179	0,0000
29	0,0750	0,0000	0,0000	0,0000	0,9250	0,0000
30	0,0686	0,0000	0,0000	0,0000	0,9314	0,0000
31	0,0627	0,0000	0,0000	0,0000	0,9373	0,0000
32	0,0573	0,0000	0,0000	0,0000	0,9427	0,0000
33	0,0524	0,0000	0,0000	0,0000	0,9476	0,0000
34	0,0479	0,0000	0,0000	0,0000	0,9521	0,0000
35	0,0438	0,0000	0,0000	0,0000	0,9562	0,0000
36	0,0400	0,0000	0,0000	0,0000	0,9600	0,0000
37	0,0366	0,0000	0,0000	0,0000	0,9634	0,0000
38	0,0335	0,0000	0,0000	0,0000	0,9665	0,0000
39	0,0306	0,0000	0,0000	0,0000	0,9694	0,0000
40	0,0280	0,0000	0,0000	0,0000	0,9720	0,0000
41	0,0256	0,0000	0,0000	0,0000	0,9744	0,0000
42	0,0234	0,0000	0,0000	0,0000	0,9766	0,0000
43	0,0214	0,0000	0,0000	0,0000	0,9786	0,0000
44	0,0195	0,0000	0,0000	0,0000	0,9805	0,0000
45	0,0179	0,0000	0,0000	0,0000	0,9821	0,0000
46	0,0163	0,0000	0,0000	0,0000	0,9837	0,0000
47	0,0149	0,0000	0,0000	0,0000	0,9851	0,0000
48	0,0136	0,0000	0,0000	0,0000	0,9864	0,0000
49	0,0125	0,0000	0,0000	0,0000	0,9875	0,0000
50	0,0114	0,0000	0,0000	0,0000	0,9886	0,0000
51	0,0104	0,0000	0,0000	0,0000	0,9896	0,0000
52	0,0095	0,0000	0,0000	0,0000	0,9905	0,0000
53	0,0087	0,0000	0,0000	0,0000	0,9913	0,0000
54	0,0080	0,0000	0,0000	0,0000	0,9920	0,0000
55	0,0073	0,0000	0,0000	0,0000	0,9927	0,0000
56	0,0067	0,0000	0,0000	0,0000	0,9933	0,0000
57	0,0061	0,0000	0,0000	0,0000	0,9939	0,0000
58	0,0056	0,0000	0,0000	0,0000	0,9944	0,0000
59	0,0051	0,0000	0,0000	0,0000	0,9949	0,0000
60	0,0047	0,0000	0,0000	0,0000	0,9953	0,0000

Table C3: 6-month (stage1) and 60-month (stage2*) Markov model event estimations for **LMWH treatment** in Low and High Risk CAT patient cohort ($n=1,000$)

*"Thrombo-Px" state is not exposed to any anticoagulants nor costs from month 7 onwards and represents the alive event free patients

VKA	Low Risk Cohort - UTILITY					
Month	Thrombo-Px	MB	VTE	CRB	Dead	Total
0	0,6450	0,0000	0,0000	0,0000	0,0000	0,65
1	0,5997	0,0042	0,0058	0,0133	0,0000	0,62
2	0,5570	0,0081	0,0113	0,0256	0,0000	0,60
3	0,5163	0,0117	0,0165	0,0373	0,0000	0,58
4	0,4776	0,0152	0,0216	0,0485	0,0000	0,56
5	0,4408	0,0184	0,0265	0,0591	0,0000	0,54
6	0,4058	0,0215	0,0311	0,0692	0,0000	0,53
7	0,4818	0,0064	0,0093	0,0208	0,0000	0,52
8	0,4943	0,0019	0,0028	0,0062	0,0000	0,51
9	0,4881	0,0006	0,0008	0,0019	0,0000	0,49
10	0,4766	0,0002	0,0003	0,0006	0,0000	0,48
11	0,4638	0,0001	0,0001	0,0002	0,0000	0,46
12	0,4508	0,0000	0,0000	0,0001	0,0000	0,45
13	0,4380	0,0000	0,0000	0,0000	0,0000	0,44
14	0,4256	0,0000	0,0000	0,0000	0,0000	0,43
15	0,4135	0,0000	0,0000	0,0000	0,0000	0,41
16	0,4017	0,0000	0,0000	0,0000	0,0000	0,40
17	0,3903	0,0000	0,0000	0,0000	0,0000	0,39
18	0,3792	0,0000	0,0000	0,0000	0,0000	0,38
19	0,3684	0,0000	0,0000	0,0000	0,0000	0,37
20	0,3579	0,0000	0,0000	0,0000	0,0000	0,36
21	0,3477	0,0000	0,0000	0,0000	0,0000	0,35
22	0,3378	0,0000	0,0000	0,0000	0,0000	0,34
23	0,3282	0,0000	0,0000	0,0000	0,0000	0,33
24	0,3189	0,0000	0,0000	0,0000	0,0000	0,32
25	0,3098	0,0000	0,0000	0,0000	0,0000	0,31
26	0,3010	0,0000	0,0000	0,0000	0,0000	0,30
27	0,2924	0,0000	0,0000	0,0000	0,0000	0,29
28	0,2841	0,0000	0,0000	0,0000	0,0000	0,28
29	0,2760	0,0000	0,0000	0,0000	0,0000	0,28
30	0,2682	0,0000	0,0000	0,0000	0,0000	0,27
31	0,2606	0,0000	0,0000	0,0000	0,0000	0,26
32	0,2531	0,0000	0,0000	0,0000	0,0000	0,25
33	0,2459	0,0000	0,0000	0,0000	0,0000	0,25
34	0,2389	0,0000	0,0000	0,0000	0,0000	0,24
35	0,2321	0,0000	0,0000	0,0000	0,0000	0,23
36	0,2255	0,0000	0,0000	0,0000	0,0000	0,23
37	0,2191	0,0000	0,0000	0,0000	0,0000	0,22
38	0,2129	0,0000	0,0000	0,0000	0,0000	0,21
39	0,2068	0,0000	0,0000	0,0000	0,0000	0,21
40	0,2010	0,0000	0,0000	0,0000	0,0000	0,20
41	0,1952	0,0000	0,0000	0,0000	0,0000	0,20
42	0,1897	0,0000	0,0000	0,0000	0,0000	0,19
43	0,1843	0,0000	0,0000	0,0000	0,0000	0,18
44	0,1790	0,0000	0,0000	0,0000	0,0000	0,18
45	0,1739	0,0000	0,0000	0,0000	0,0000	0,17
46	0,1690	0,0000	0,0000	0,0000	0,0000	0,17
47	0,1642	0,0000	0,0000	0,0000	0,0000	0,16
48	0,1595	0,0000	0,0000	0,0000	0,0000	0,16
49	0,1550	0,0000	0,0000	0,0000	0,0000	0,15
50	0,1506	0,0000	0,0000	0,0000	0,0000	0,15
51	0,1463	0,0000	0,0000	0,0000	0,0000	0,15
52	0,1421	0,0000	0,0000	0,0000	0,0000	0,14
53	0,1381	0,0000	0,0000	0,0000	0,0000	0,14
54	0,1342	0,0000	0,0000	0,0000	0,0000	0,13
55	0,1303	0,0000	0,0000	0,0000	0,0000	0,13
56	0,1266	0,0000	0,0000	0,0000	0,0000	0,13
57	0,1230	0,0000	0,0000	0,0000	0,0000	0,12
58	0,1195	0,0000	0,0000	0,0000	0,0000	0,12
59	0,1161	0,0000	0,0000	0,0000	0,0000	0,12
60	0,1128	0,0000	0,0000	0,0000	0,0000	0,11
Total	18,0420	0,0883	0,1261	0,2827	0,0000	18,54

VKA	Low Risk Cohort - UTILITY					
Month	Thrombo-Px	MB	VTE	CRB	Dead	Total
0	0,6450	0,0000	0,0000	0,0000	0,0000	0,65
1	0,5425	0,0065	0,0125	0,0199	0,0000	0,58
2	0,4743	0,0120	0,0236	0,0168	0,0000	0,53
3	0,4141	0,0166	0,0334	0,0147	0,0000	0,48
4	0,3616	0,0206	0,0421	0,0128	0,0000	0,44
5	0,3157	0,0239	0,0499	0,0112	0,0000	0,40
6	0,2757	0,0266	0,0567	0,0098	0,0000	0,37
7	0,2913	0,0080	0,0170	0,0255	0,0000	0,34
8	0,2990	0,0024	0,0051	0,0077	0,0000	0,31
9	0,2827	0,0007	0,0015	0,0023	0,0000	0,29
10	0,2609	0,0002	0,0005	0,0007	0,0000	0,26
11	0,2389	0,0001	0,0001	0,0002	0,0000	0,24
12	0,2182	0,0000	0,0000	0,0001	0,0000	0,22
13	0,1991	0,0000	0,0000	0,0000	0,0000	0,20
14	0,1817	0,0000	0,0000	0,0000	0,0000	0,18
15	0,1657	0,0000	0,0000	0,0000	0,0000	0,17
16	0,1512	0,0000	0,0000	0,0000	0,0000	0,15
17	0,1379	0,0000	0,0000	0,0000	0,0000	0,14
18	0,1258	0,0000	0,0000	0,0000	0,0000	0,13
19	0,1148	0,0000	0,0000	0,0000	0,0000	0,11
20	0,1047	0,0000	0,0000	0,0000	0,0000	0,10
21	0,0955	0,0000	0,0000	0,0000	0,0000	0,10
22	0,0871	0,0000	0,0000	0,0000	0,0000	0,09
23	0,0795	0,0000	0,0000	0,0000	0,0000	0,08
24	0,0725	0,0000	0,0000	0,0000	0,0000	0,07
25	0,0661	0,0000	0,0000	0,0000	0,0000	0,07
26	0,0603	0,0000	0,0000	0,0000	0,0000	0,06
27	0,0550	0,0000	0,0000	0,0000	0,0000	0,06
28	0,0502	0,0000	0,0000	0,0000	0,0000	0,05
29	0,0458	0,0000	0,0000	0,0000	0,0000	0,05
30	0,0418	0,0000	0,0000	0,0000	0,0000	0,04
31	0,0381	0,0000	0,0000	0,0000	0,0000	0,04
32	0,0348	0,0000	0,0000	0,0000	0,0000	0,03
33	0,0317	0,0000	0,0000	0,0000	0,0000	0,03
34	0,0289	0,0000	0,0000	0,0000	0,0000	0,03
35	0,0264	0,0000	0,0000	0,0000	0,0000	0,03
36	0,0241	0,0000	0,0000	0,0000	0,0000	0,02
37	0,0220	0,0000	0,0000	0,0000	0,0000	0,02
38	0,0200	0,0000	0,0000	0,0000	0,0000	0,02
39	0,0183	0,0000	0,0000	0,0000	0,0000	0,02
40	0,0167	0,0000	0,0000	0,0000	0,0000	0,02
41	0,0152	0,0000	0,0000	0,0000	0,0000	0,02
42	0,0139	0,0000	0,0000	0,0000	0,0000	0,01
43	0,0127	0,0000	0,0000	0,0000	0,0000	0,01
44	0,0115	0,0000	0,0000	0,0000	0,0000	0,01
45	0,0105	0,0000	0,0000	0,0000	0,0000	0,01
46	0,0096	0,0000	0,0000	0,0000	0,0000	0,01
47	0,0088	0,0000	0,0000	0,0000	0,0000	0,01
48	0,0080	0,0000	0,0000	0,0000	0,0000	0,01
49	0,0073	0,0000	0,0000	0,0000	0,0000	0,01
50	0,0066	0,0000	0,0000	0,0000	0,0000	0,01
51	0,0061	0,0000	0,0000	0,0000	0,0000	0,01
52	0,0055	0,0000	0,0000	0,0000	0,0000	0,01
53	0,0050	0,0000	0,0000	0,0000	0,0000	0,01
54	0,0046	0,0000	0,0000	0,0000	0,0000	0,00
55	0,0042	0,0000	0,0000	0,0000	0,0000	0,00
56	0,0038	0,0000	0,0000	0,0000	0,0000	0,00
57	0,0035	0,0000	0,0000	0,0000	0,0000	0,00
58	0,0032	0,0000	0,0000	0,0000	0,0000	0,00
59	0,0029	0,0000	0,0000	0,0000	0,0000	0,00
60	0,0027	0,0000	0,0000	0,0000	0,0000	0,00
Total	6,8613	0,1175	0,2427	0,1216	0,0000	7,34

Table D1: 60-month* Markov model **Utility** projection for **VKA treatment** in Low and High Risk CAT patient cohort (n=1,00)

*"Thrombo-Px" state from month 7 onwards is not exposed to any anticoagulants and represents the utility of all alive and event free patients

DOAC	Low Risk Cohort - UTILITY					
Month	Thrombo-Px	MB	VTE	CRB	Dead	Total
0	0,6450	0,0000	0,0000	0,0000	0,0000	0,645
1	0,6068	0,0030	0,0037	0,0123	0,0000	0,626
2	0,5704	0,0058	0,0073	0,0238	0,0000	0,607
3	0,5354	0,0086	0,0108	0,0349	0,0000	0,590
4	0,5018	0,0112	0,0142	0,0455	0,0000	0,573
5	0,4696	0,0136	0,0175	0,0557	0,0000	0,556
6	0,4386	0,0160	0,0206	0,0655	0,0000	0,541
7	0,5006	0,0048	0,0062	0,0197	0,0000	0,531
8	0,5098	0,0014	0,0019	0,0059	0,0000	0,519
9	0,5033	0,0004	0,0006	0,0018	0,0000	0,506
10	0,4924	0,0001	0,0002	0,0005	0,0000	0,493
11	0,4804	0,0000	0,0001	0,0002	0,0000	0,481
12	0,4683	0,0000	0,0000	0,0000	0,0000	0,468
13	0,4563	0,0000	0,0000	0,0000	0,0000	0,456
14	0,4447	0,0000	0,0000	0,0000	0,0000	0,445
15	0,4333	0,0000	0,0000	0,0000	0,0000	0,433
16	0,4222	0,0000	0,0000	0,0000	0,0000	0,422
17	0,4114	0,0000	0,0000	0,0000	0,0000	0,411
18	0,4008	0,0000	0,0000	0,0000	0,0000	0,401
19	0,3906	0,0000	0,0000	0,0000	0,0000	0,391
20	0,3806	0,0000	0,0000	0,0000	0,0000	0,381
21	0,3708	0,0000	0,0000	0,0000	0,0000	0,371
22	0,3613	0,0000	0,0000	0,0000	0,0000	0,361
23	0,3521	0,0000	0,0000	0,0000	0,0000	0,352
24	0,3431	0,0000	0,0000	0,0000	0,0000	0,343
25	0,3343	0,0000	0,0000	0,0000	0,0000	0,334
26	0,3257	0,0000	0,0000	0,0000	0,0000	0,326
27	0,3174	0,0000	0,0000	0,0000	0,0000	0,317
28	0,3093	0,0000	0,0000	0,0000	0,0000	0,309
29	0,3013	0,0000	0,0000	0,0000	0,0000	0,301
30	0,2936	0,0000	0,0000	0,0000	0,0000	0,294
31	0,2861	0,0000	0,0000	0,0000	0,0000	0,286
32	0,2788	0,0000	0,0000	0,0000	0,0000	0,279
33	0,2716	0,0000	0,0000	0,0000	0,0000	0,272
34	0,2647	0,0000	0,0000	0,0000	0,0000	0,265
35	0,2579	0,0000	0,0000	0,0000	0,0000	0,258
36	0,2513	0,0000	0,0000	0,0000	0,0000	0,251
37	0,2449	0,0000	0,0000	0,0000	0,0000	0,245
38	0,2386	0,0000	0,0000	0,0000	0,0000	0,239
39	0,2325	0,0000	0,0000	0,0000	0,0000	0,232
40	0,2265	0,0000	0,0000	0,0000	0,0000	0,227
41	0,2207	0,0000	0,0000	0,0000	0,0000	0,221
42	0,2151	0,0000	0,0000	0,0000	0,0000	0,215
43	0,2096	0,0000	0,0000	0,0000	0,0000	0,210
44	0,2042	0,0000	0,0000	0,0000	0,0000	0,204
45	0,1990	0,0000	0,0000	0,0000	0,0000	0,199
46	0,1939	0,0000	0,0000	0,0000	0,0000	0,194
47	0,1889	0,0000	0,0000	0,0000	0,0000	0,189
48	0,1841	0,0000	0,0000	0,0000	0,0000	0,184
49	0,1794	0,0000	0,0000	0,0000	0,0000	0,179
50	0,1748	0,0000	0,0000	0,0000	0,0000	0,175
51	0,1703	0,0000	0,0000	0,0000	0,0000	0,170
52	0,1659	0,0000	0,0000	0,0000	0,0000	0,166
53	0,1617	0,0000	0,0000	0,0000	0,0000	0,162
54	0,1576	0,0000	0,0000	0,0000	0,0000	0,158
55	0,1535	0,0000	0,0000	0,0000	0,0000	0,154
56	0,1496	0,0000	0,0000	0,0000	0,0000	0,150
57	0,1458	0,0000	0,0000	0,0000	0,0000	0,146
58	0,1420	0,0000	0,0000	0,0000	0,0000	0,142
59	0,1384	0,0000	0,0000	0,0000	0,0000	0,138
60	0,1349	0,0000	0,0000	0,0000	0,0000	0,135
Total	19,4133	0,0650	0,0830	0,2657	0,0000	19,827

DOAC	Low Risk Cohort - UTILITY					
Month	Thrombo-Px	MB	VTE	CRB	Dead	Total
0	0,6450	0,0000	0,0000	0,0000	0,0000	0,645
1	0,5304	0,0120	0,0049	0,0336	0,0000	0,581
2	0,4319	0,0225	0,0093	0,0613	0,0000	0,525
3	0,3454	0,0315	0,0132	0,0856	0,0000	0,476
4	0,2697	0,0394	0,0168	0,1069	0,0000	0,433
5	0,2033	0,0461	0,0200	0,1256	0,0000	0,395
6	0,1451	0,0520	0,0229	0,1420	0,0000	0,362
7	0,2727	0,0156	0,0069	0,0426	0,0000	0,338
8	0,2908	0,0047	0,0021	0,0128	0,0000	0,310
9	0,2777	0,0014	0,0006	0,0038	0,0000	0,284
10	0,2570	0,0004	0,0002	0,0012	0,0000	0,259
11	0,2354	0,0001	0,0001	0,0003	0,0000	0,236
12	0,2149	0,0000	0,0000	0,0001	0,0000	0,215
13	0,1960	0,0000	0,0000	0,0000	0,0000	0,196
14	0,1787	0,0000	0,0000	0,0000	0,0000	0,179
15	0,1630	0,0000	0,0000	0,0000	0,0000	0,163
16	0,1486	0,0000	0,0000	0,0000	0,0000	0,149
17	0,1354	0,0000	0,0000	0,0000	0,0000	0,135
18	0,1235	0,0000	0,0000	0,0000	0,0000	0,123
19	0,1126	0,0000	0,0000	0,0000	0,0000	0,113
20	0,1026	0,0000	0,0000	0,0000	0,0000	0,103
21	0,0935	0,0000	0,0000	0,0000	0,0000	0,094
22	0,0853	0,0000	0,0000	0,0000	0,0000	0,085
23	0,0777	0,0000	0,0000	0,0000	0,0000	0,078
24	0,0709	0,0000	0,0000	0,0000	0,0000	0,071
25	0,0646	0,0000	0,0000	0,0000	0,0000	0,065
26	0,0589	0,0000	0,0000	0,0000	0,0000	0,059
27	0,0537	0,0000	0,0000	0,0000	0,0000	0,054
28	0,0489	0,0000	0,0000	0,0000	0,0000	0,049
29	0,0446	0,0000	0,0000	0,0000	0,0000	0,045
30	0,0407	0,0000	0,0000	0,0000	0,0000	0,041
31	0,0371	0,0000	0,0000	0,0000	0,0000	0,037
32	0,0338	0,0000	0,0000	0,0000	0,0000	0,034
33	0,0308	0,0000	0,0000	0,0000	0,0000	0,031
34	0,0281	0,0000	0,0000	0,0000	0,0000	0,028
35	0,0256	0,0000	0,0000	0,0000	0,0000	0,026
36	0,0233	0,0000	0,0000	0,0000	0,0000	0,023
37	0,0213	0,0000	0,0000	0,0000	0,0000	0,021
38	0,0194	0,0000	0,0000	0,0000	0,0000	0,019
39	0,0177	0,0000	0,0000	0,0000	0,0000	0,018
40	0,0161	0,0000	0,0000	0,0000	0,0000	0,016
41	0,0147	0,0000	0,0000	0,0000	0,0000	0,015
42	0,0134	0,0000	0,0000	0,0000	0,0000	0,013
43	0,0122	0,0000	0,0000	0,0000	0,0000	0,012
44	0,0111	0,0000	0,0000	0,0000	0,0000	0,011
45	0,0102	0,0000	0,0000	0,0000	0,0000	0,010
46	0,0093	0,0000	0,0000	0,0000	0,0000	0,009
47	0,0084	0,0000	0,0000	0,0000	0,0000	0,008
48	0,0077	0,0000	0,0000	0,0000	0,0000	0,008
49	0,0070	0,0000	0,0000	0,0000	0,0000	0,007
50	0,0064	0,0000	0,0000	0,0000	0,0000	0,006
51	0,0058	0,0000	0,0000	0,0000	0,0000	0,006
52	0,0053	0,0000	0,0000	0,0000	0,0000	0,005
53	0,0048	0,0000	0,0000	0,0000	0,0000	0,005
54	0,0044	0,0000	0,0000	0,0000	0,0000	0,004
55	0,0040	0,0000	0,0000	0,0000	0,0000	0,004
56	0,0037	0,0000	0,0000	0,0000	0,0000	0,004
57	0,0033	0,0000	0,0000	0,0000	0,0000	0,003
58	0,0030	0,0000	0,0000	0,0000	0,0000	0,003
59	0,0028	0,0000	0,0000	0,0000	0,0000	0,003
60	0,0025	0,0000	0,0000	0,0000	0,0000	0,003
Total	6,3119	0,2258	0,0969	0,6159	0,0000	7,250

Table D2: 60-month* Markov model **Utility** projection for **DOAC treatment** in Low and High Risk CAT patient cohort (n=1,00)

*"Thrombo-Px" state from month 7 onwards is not exposed to any anticoagulants and represents the utility of all alive and event free patients

Low Risk Cohort - UTILITY						
Month	Thrombo-Px	MB	VTE	CRB	Dead	Total
0	0,645	0,000	0,000	0,000	0,000	0,65
1	0,606	0,003	0,004	0,012	0,000	0,63
2	0,569	0,006	0,008	0,024	0,000	0,61
3	0,533	0,009	0,012	0,035	0,000	0,59
4	0,499	0,012	0,015	0,045	0,000	0,57
5	0,466	0,015	0,019	0,056	0,000	0,56
6	0,435	0,017	0,022	0,065	0,000	0,54
7	0,499	0,005	0,007	0,020	0,000	0,53
8	0,509	0,002	0,002	0,006	0,000	0,52
9	0,503	0,000	0,001	0,002	0,000	0,51
10	0,492	0,000	0,000	0,001	0,000	0,49
11	0,480	0,000	0,000	0,000	0,000	0,48
12	0,468	0,000	0,000	0,000	0,000	0,47
13	0,456	0,000	0,000	0,000	0,000	0,46
14	0,444	0,000	0,000	0,000	0,000	0,44
15	0,433	0,000	0,000	0,000	0,000	0,43
16	0,422	0,000	0,000	0,000	0,000	0,42
17	0,411	0,000	0,000	0,000	0,000	0,41
18	0,401	0,000	0,000	0,000	0,000	0,40
19	0,390	0,000	0,000	0,000	0,000	0,39
20	0,380	0,000	0,000	0,000	0,000	0,38
21	0,371	0,000	0,000	0,000	0,000	0,37
22	0,361	0,000	0,000	0,000	0,000	0,36
23	0,352	0,000	0,000	0,000	0,000	0,35
24	0,343	0,000	0,000	0,000	0,000	0,34
25	0,334	0,000	0,000	0,000	0,000	0,33
26	0,325	0,000	0,000	0,000	0,000	0,33
27	0,317	0,000	0,000	0,000	0,000	0,32
28	0,309	0,000	0,000	0,000	0,000	0,31
29	0,301	0,000	0,000	0,000	0,000	0,30
30	0,293	0,000	0,000	0,000	0,000	0,29
31	0,286	0,000	0,000	0,000	0,000	0,29
32	0,279	0,000	0,000	0,000	0,000	0,28
33	0,271	0,000	0,000	0,000	0,000	0,27
34	0,264	0,000	0,000	0,000	0,000	0,26
35	0,258	0,000	0,000	0,000	0,000	0,26
36	0,251	0,000	0,000	0,000	0,000	0,25
37	0,245	0,000	0,000	0,000	0,000	0,24
38	0,238	0,000	0,000	0,000	0,000	0,24
39	0,232	0,000	0,000	0,000	0,000	0,23
40	0,226	0,000	0,000	0,000	0,000	0,23
41	0,221	0,000	0,000	0,000	0,000	0,22
42	0,215	0,000	0,000	0,000	0,000	0,21
43	0,209	0,000	0,000	0,000	0,000	0,21
44	0,204	0,000	0,000	0,000	0,000	0,20
45	0,199	0,000	0,000	0,000	0,000	0,20
46	0,194	0,000	0,000	0,000	0,000	0,19
47	0,189	0,000	0,000	0,000	0,000	0,19
48	0,184	0,000	0,000	0,000	0,000	0,18
49	0,179	0,000	0,000	0,000	0,000	0,18
50	0,175	0,000	0,000	0,000	0,000	0,17
51	0,170	0,000	0,000	0,000	0,000	0,17
52	0,166	0,000	0,000	0,000	0,000	0,17
53	0,162	0,000	0,000	0,000	0,000	0,16
54	0,157	0,000	0,000	0,000	0,000	0,16
55	0,153	0,000	0,000	0,000	0,000	0,15
56	0,149	0,000	0,000	0,000	0,000	0,15
57	0,146	0,000	0,000	0,000	0,000	0,15
58	0,142	0,000	0,000	0,000	0,000	0,14
59	0,138	0,000	0,000	0,000	0,000	0,14
60	0,135	0,000	0,000	0,000	0,000	0,13
Total	19,39	0,07	0,09	0,27	0,00	19,81

Low Risk Cohort - UTILITY						
Month	Thrombo-Px	MB	VTE	CRB	Dead	Total
0	0,645	0,000	0,000	0,000	0,000	0,65
1	0,555	0,007	0,008	0,015	0,000	0,58
2	0,476	0,013	0,014	0,027	0,000	0,53
3	0,407	0,018	0,020	0,038	0,000	0,48
4	0,345	0,023	0,026	0,048	0,000	0,44
5	0,290	0,027	0,031	0,057	0,000	0,40
6	0,242	0,030	0,035	0,064	0,000	0,37
7	0,307	0,009	0,011	0,019	0,000	0,35
8	0,306	0,003	0,003	0,006	0,000	0,32
9	0,287	0,001	0,001	0,002	0,000	0,29
10	0,265	0,000	0,000	0,001	0,000	0,27
11	0,243	0,000	0,000	0,000	0,000	0,24
12	0,222	0,000	0,000	0,000	0,000	0,22
13	0,203	0,000	0,000	0,000	0,000	0,20
14	0,186	0,000	0,000	0,000	0,000	0,19
15	0,170	0,000	0,000	0,000	0,000	0,17
16	0,155	0,000	0,000	0,000	0,000	0,16
17	0,142	0,000	0,000	0,000	0,000	0,14
18	0,130	0,000	0,000	0,000	0,000	0,13
19	0,119	0,000	0,000	0,000	0,000	0,12
20	0,109	0,000	0,000	0,000	0,000	0,11
21	0,099	0,000	0,000	0,000	0,000	0,10
22	0,091	0,000	0,000	0,000	0,000	0,09
23	0,083	0,000	0,000	0,000	0,000	0,08
24	0,076	0,000	0,000	0,000	0,000	0,08
25	0,069	0,000	0,000	0,000	0,000	0,07
26	0,063	0,000	0,000	0,000	0,000	0,06
27	0,058	0,000	0,000	0,000	0,000	0,06
28	0,053	0,000	0,000	0,000	0,000	0,05
29	0,048	0,000	0,000	0,000	0,000	0,05
30	0,044	0,000	0,000	0,000	0,000	0,04
31	0,040	0,000	0,000	0,000	0,000	0,04
32	0,037	0,000	0,000	0,000	0,000	0,04
33	0,034	0,000	0,000	0,000	0,000	0,03
34	0,031	0,000	0,000	0,000	0,000	0,03
35	0,028	0,000	0,000	0,000	0,000	0,03
36	0,026	0,000	0,000	0,000	0,000	0,03
37	0,024	0,000	0,000	0,000	0,000	0,02
38	0,022	0,000	0,000	0,000	0,000	0,02
39	0,020	0,000	0,000	0,000	0,000	0,02
40	0,018	0,000	0,000	0,000	0,000	0,02
41	0,016	0,000	0,000	0,000	0,000	0,02
42	0,015	0,000	0,000	0,000	0,000	0,02
43	0,014	0,000	0,000	0,000	0,000	0,01
44	0,013	0,000	0,000	0,000	0,000	0,01
45	0,012	0,000	0,000	0,000	0,000	0,01
46	0,011	0,000	0,000	0,000	0,000	0,01
47	0,010	0,000	0,000	0,000	0,000	0,01
48	0,009	0,000	0,000	0,000	0,000	0,01
49	0,008	0,000	0,000	0,000	0,000	0,01
50	0,007	0,000	0,000	0,000	0,000	0,01
51	0,007	0,000	0,000	0,000	0,000	0,01
52	0,006	0,000	0,000	0,000	0,000	0,01
53	0,006	0,000	0,000	0,000	0,000	0,01
54	0,005	0,000	0,000	0,000	0,000	0,01
55	0,005	0,000	0,000	0,000	0,000	0,00
56	0,004	0,000	0,000	0,000	0,000	0,00
57	0,004	0,000	0,000	0,000	0,000	0,00
58	0,004	0,000	0,000	0,000	0,000	0,00
59	0,003	0,000	0,000	0,000	0,000	0,00
60	0,003	0,000	0,000	0,000	0,000	0,00
Total	6,93	0,13	0,15	0,28	0,00	7,48

Table D3: 60-month* Markov model **Utility** projection for **LWH treatment** in Low and High Risk CAT patient cohort (n=1,00)

*"Thrombo-Px" state from month 7 onwards is not exposed to any anticoagulants and represents the utility of all alive and event free patients

Anticoagulant Class	Agent	Brand name	SmPC dosing (month 1)	SmPC dosing (month 2-6)	Average Patient Weight	DDD Required (month 1)	DDD Required (month 2-6)	Forms per day Required (month 1)	Forms per day Required (month 2-6)
LMWH	Tinzaparin	innohep®		175IU/Kg/24h			13.125 IU	14.000 IU Syringes (OD)	
	Enoxaparin	Clexane®		100mg/kg/12h	75 Kg		15.000 IU	2 x 8.000 IU (80mg) Syringes	
	Dalteparin	Fragmin®	200IU/kg/day	150IU/kg/day		15.000 IU	11.250 IU	2 x 7.500 IU Syringes	1 x 7500 IU Syr + 1 x 5.000 IU Syr
	Rivaroxaban	Xarelto®	15mg/12h (21d)	15mg/24h		30 mg (21d)	15 mg	2 x 15 mg (21d)	1 x 15mg
	Apixaban	Eliquis®	5mg/12h (14d)	5mg/24h	N/A - dosing independent from weight	10 mg (14d)	5 mg	2 x 5 mg (14d)	1 x 5 mg
DOAC	Dabigatran	Pradaxa®	150mg/12h (after 5d of LMWH)				300 mg	2 x 150 mg	
	Edoxaban	Lixiana®	60mg/24h (after 5d of LMWH)				60 mg		1 x 60 mg
VKA	Sintrom	Sintrom(r)	4-8mg/24h (after 5d of LMWH)		N/A - dosing independent from weight		6 mg		1,5 x 4 mg
	Panwarfarin	Panwarfin®	2-10mg/24h (after 5d of LMWH)				7 mg		1,4 x 5 mg

Table E1: Available anticoagulant brands within all classes (VKA, DOAC & LMWH) in the Greek hospital market and estimated DDD for CAT accounting SmPC posology in different timeframes (Month 1 and Month 2-6) for long term anticoagulation

Xarelto®	20mg in 28s	20mg in 100s	15mg in 28s	15mg in 42s	15mg in 100s	14000 IU in 2s	14000 IU in 10s
Pack Cost	47,28 €	229,91 €	47,55 €	96,57 €	229,91 €	14,70 €	75,99 €
Tab Cost	1,69 €	2,30 €	1,70 €	2,30 €	2,30 €	7,35 €	7,60 €
Avg Tab Cost	1,99 €			2,10 €			7,47 €
Month 1 Total			102,11 €				209,29 €
Month 1 DDD			3,65 €			7,47 €	
Month 2-6 DDD			1,99 €			7,47 €	
https://www.galinos.gr/web/drugs/main/drugs/xarelto							
Eliquis®	5mg in 100s	5mg in 60s	5mg in 28s				
Pack Cost	112,25 €	74,43 €	39,33 €				
Tab Cost		1,24 €	1,40 €				
Avg Tab Cost		1,32 €					
Month 1 Total		64,81 €				166,54 €	
Month 1 DDD		2,31 €				5,95 €	
Month 2-6 DDD		2,65 €				5,95 €	
https://www.galinos.gr/web/drugs/main/drugs/ellaquis							
Pradaxa®	150mg in 60s						
Pack Cost		51,08 €					
Tab Cost		0,85 €					
Avg Tab Cost		0,85 €					
Month 1 Total		23,84 €				140,45 €	119,48 €
Month 1 DDD		1,70 €				5,02 €	-
Month 2-6 DDD		1,70 €				-	4,27 €
https://www.galinos.gr/web/drugs/main/drugs/pradaxa							
Lixiana®	60mg in 30s						
Pack Cost		53,01 €					
Tab Cost		1,77 €					
Avg Tab Cost		1,77 €					
Month 1 Total		49,48 €				1,51 €	
Month 1 DDD		1,77 €				0,08 €	
Month 2-6 DDD		1,77 €				0,08 €	
https://www.galinos.gr/web/drugs/main/drugs/lixiana							
innovep®							
Pack Cost							
Syringe Cost							
Avg Syr. Cost							
Month 1 Avg							
Month 1 DDD							
Month 2-6 DDD							
https://www.galinos.gr/web/drugs/main/drugs/innovep							
clexane®							
Pack Cost							
Syringe Cost							
Avg Syr. Cost							
Month 1 Avg							
Month 1 DDD							
Month 2-6 DDD							
https://www.galinos.gr/web/drugs/main/drugs/clexane							
Fragmin®							
Pack Cost							
Syringe Cost							
Avg Syr. Cost							
Month 1 Avg							
Month 1 DDD							
Month 2-6 DDD							
https://www.galinos.gr/web/drugs/main/drugs/fragmin							
Sintrom®	4mg in 20s						
Pack Cost							
Tab Cost							
Avg Tab Cost							
Month 1 Total							
Month 1 DDD							
Month 2-6 DDD							
https://www.galinos.gr/web/drugs/main/drugs/sintrom							
Panwarfin®	5mg in 20s						
Pack Cost							
Tab Cost							
Avg Tab Cost							
Month 1 Total							
Month 1 DDD							
Month 2-6 DDD							
https://www.galinos.gr/web/drugs/main/drugs/panwarfin							

Table E2: Available packs and estimated DDD costs of different anticoagulant brands within all classes (VKA, DOAC & LMWH) in the Greek hospital market for CAT accounting SmPC posology

VKA	VKA Low Risk Cohort Costs					
Cycle (30d)	Drug Thrombo-prophylaxis	Secondary Medical Support	Major Bleeding	Venous Thrombo Embolism	Clinical Relevant (non major) Bleeding	Total
0	- €	- €	- €	- €	- €	- €
1	32 €	84 €	7 €	17 €	8 €	147 €
2	3 €	60 €	6 €	16 €	7 €	93 €
3	3 €	29 €	6 €	16 €	7 €	60 €
4	2 €	27 €	5 €	15 €	7 €	57 €
5	2 €	17 €	5 €	14 €	6 €	45 €
6	2 €	9 €	5 €	14 €	6 €	36 €
Class Total	44 €	225 €	34 €	92 €	42 €	437 €

DOAC	DOAC Low Risk Cohort Costs					
Cycle (30d)	Drug Thrombo-prophylaxis	Secondary Medical Support	Major Bleeding	Venous Thrombo Embolism	Clinical Relevant (non major) Bleeding	Total
0	- €	- €	- €	- €	- €	- €
1	79 €	- €	5 €	11 €	7 €	102 €
2	56 €	- €	4 €	11 €	7 €	78 €
3	54 €	- €	4 €	10 €	7 €	75 €
4	52 €	- €	4 €	10 €	6 €	72 €
5	50 €	- €	4 €	10 €	6 €	69 €
6	48 €	- €	4 €	9 €	6 €	67 €
Class Total	338 €	- €	25 €	61 €	40 €	463 €

LMWH	LMWH Low Risk Cohort Costs					
Cycle (30d)	Drug Thrombo-prophylaxis	Secondary Medical Support	Major Bleeding	Venous Thrombo Embolism	Clinical Relevant (non major) Bleeding	Total
0	- €	- €	- €	- €	- €	- €
1	178 €	- €	5 €	12 €	7 €	202 €
2	164 €	- €	5 €	11 €	7 €	187 €
3	157 €	- €	5 €	11 €	7 €	180 €
4	151 €	- €	4 €	11 €	6 €	172 €
5	145 €	- €	4 €	10 €	6 €	165 €
6	139 €	- €	4 €	10 €	6 €	159 €
Class Total	934 €	- €	28 €	65 €	39 €	1.066 €

Table F1: Estimated average costs of different anticoagulation classes (VKA, DOAC & LMWH) under 6 months treatment in **Low Risk CAT** patient Markov model cohort ($n=1,000$)

VKA		VKA High Risk Cohort Costs				
Cycle (30d)	Drug Thrombo-prophylaxis	Secondary Medical Support	Major Bleeding	Venous Thrombo Embolism	Clinical Relevant (non major) Bleeding	Total
0	- €	- €	- €	- €	- €	- €
1	30 €	76 €	10 €	37 €	12 €	165 €
2	2 €	50 €	9 €	33 €	10 €	104 €
3	2 €	22 €	7 €	29 €	9 €	69 €
4	2 €	19 €	6 €	26 €	8 €	60 €
5	2 €	11 €	5 €	23 €	7 €	47 €
6	1 €	5 €	4 €	20 €	6 €	37 €
Class Total	38 €	182 €	42 €	167 €	51 €	482 €

DOAC		DOAC High Risk Cohort Costs				
Cycle (30d)	Drug Thrombo-prophylaxis	Secondary Medical Support	Major Bleeding	Venous Thrombo Embolism	Clinical Relevant (non major) Bleeding	Total
0	- €	- €	- €	- €	- €	- €
1	72 €	- €	19 €	14 €	20 €	125 €
2	47 €	- €	16 €	13 €	17 €	93 €
3	41 €	- €	14 €	12 €	15 €	82 €
4	36 €	- €	12 €	10 €	13 €	72 €
5	31 €	- €	11 €	9 €	11 €	63 €
6	28 €	- €	9 €	9 €	10 €	55 €
Class Total	254 €	- €	82 €	68 €	86 €	489 €

LMWH		LMWH High Risk Cohort Costs				
Cycle (30d)	Drug Thrombo-prophylaxis	Secondary Medical Support	Major Bleeding	Venous Thrombo Embolism	Clinical Relevant (non major) Bleeding	Total
0	- €	- €	- €	- €	- €	- €
1	164 €	- €	11 €	22 €	9 €	206 €
2	139 €	- €	9 €	20 €	8 €	176 €
3	123 €	- €	8 €	18 €	7 €	156 €
4	109 €	- €	7 €	16 €	6 €	138 €
5	96 €	- €	6 €	14 €	5 €	122 €
6	85 €	- €	5 €	13 €	5 €	108 €
Class Total	717 €	- €	47 €	103 €	39 €	907 €

Table F2: Estimated average costs of different anticoagulation classes (VKA, DOAC & LMWH) under 6 months treatment in **High Risk CAT** patient Markov model cohort ($n=1,00$)



ΕΦΗΜΕΡΙΣ ΤΗΣ ΚΥΒΕΡΝΗΣΕΩΣ
ΤΗΣ ΕΛΛΗΝΙΚΗΣ ΔΗΜΟΚΡΑΤΙΑΣ

EFİ AİAZ KAI KÖNNEKTEKİZ ALVANIZZI - V. OİKONOMİKON

Table G: Published DRG costs (*Journal of governance of the Hellenic republic, law act 946/2012*) reimbursed by the national universal healthcare provider (EOPPY) in Greece

ΕΦΗΜΕΡΙΣ ΤΗΣ ΚΥΒΕΡΝΗΣΕΩΣ (ΤΕΥΧΟΣ ΔΕΥΤΕΡΟ)

16533

ΕΦΗΜΕΡΙΣ ΤΗΣ ΚΥΒΕΡΝΗΣΕΩΣ (ΤΕΥΧΟΣ ΔΕΥΤΕΡΟ)

16529

Table G: Published DRG costs (Official Government Gazette of the Hellenic republic, law act 946/2012) reimbursed by the national universal healthcare provider (EOPPY) in Greece (cont'd)

ΚΩΔ. ΚΕΝ	ΚΕΝ ΤΕΡΗ ΡΑΦΗ	ΜΔΝ από 1/3/2012	Κέρδος από 1/3/2012
Π06A	Επειδηματικό πυλωρίσμα τουγάνη	3 1.007 €	5 2.629 €
Π07M	Συναήγορος δικτύοι με καταστροφικές ουσιαστικής ή ασθματικής συνιτιδύωσης παθήσεις - επιπλοές	5 1.409 €	1 2.227 €
Π107X	Συναήγορος δικτύοι χωρίς καταστροφικές παθήσεις - επιπλοές	2 764 €	7 2123 €
Π10M	Επειδηματική οήλης (βιουβιωνής) ουρανούργων κτλ.) σε αυστηρόσυστας	4 1.697 €	2 1.045 €
Π10X	Επειδηματική οήλης (βιουβιωνής) ουρανούργων κτλ.) χωρίς αυστηρόσυστας παθήσεις - επιπλοές	2 868 €	2 1.045 €
Π11A	Επειδηματικός ποικιλής χώρας και κοιλοστοιχίες	4 514 €	3 2903 €
Π12Ma	Αλεις χαρούγενος επειδηματικός πεπτικός αυστηρόσυστας με καταστροφικές (ουσιαστικής αυστηρόσυστας παθήσεις - επιπλοές	16 3.797 €	1 691 €
Π12mB	Αλεις χαρούγενος επειδηματικός πεπτικός αυστηρόσυστας με ασθματική ή μετατροπής συνιτιδύωσης παθήσεις - επιπλοές	7 1757 €	13 2187 €
Π12X	Αλεις χαρούγενος επειδηματικός πεπτικός αυστηρόσυστας παθήσεις - επιπλοές	3 879 €	4 1358 €
Π12M	Σύνθετη ενδοστοιχίη ανώτερου πεπτικού σε καταστροφικές (ουσιαστικής αυστηρόσυστας παθήσεις - επιπλοές	12 2.000 €	11 7348 €
Π12mM	Σύνθετη ενδοστοιχίη ανώτερου πεπτικού σε παθήσεις χωρίς καταστροφικές (ουσιαστικής αυστηρόσυστας παθήσεις - επιπλοές	5 378 €	11 5.401 €
Π12XK	Σύνθετη ενδοστοιχίη ανώτερου πεπτικού σε παθήσεις χωρίς καταστροφικές (ουσιαστικής αυστηρόσυστας παθήσεις - επιπλοές	3 600 €	6 3.649 €
Π129A	Σύνθετη ενδοστοιχίη ανώτερου πεπτικού, πλειοήνα νοσηλεύσια	1 180 €	8 1.653 €
Π129M	Ενδοστοιχίη κατά τροφή σε καταστροφικές (ουσιαστικής αυστηρόσυστας παθήσεις - επιπλοές	10 1.100 €	8 1.653 €
Π129X	Ενδοστοιχίη κατά τροφή σε πεπτικό σε παθήσεις χωρίς καταστροφικές (ουσιαστικής αυστηρόσυστας παθήσεις - επιπλοές	3 600 €	4 1.078 €
Π129A	Ενδοστοιχίη κατά τροφή σε πεπτικό συστήμα	1 150 €	1 498 €
Π141M	Αιμορραγία για τραχειακούς καρδιακούς παθήσεις - επιπλοές	5 634 €	5 577 €
Π141X	Αιμορραγία για τραχειακούς καρδιακούς παθήσεις (ουσιαστικής ή συναήγορης αυστηρόσυστας παθήσεις - επιπλοές	2 375 €	8 1.875 €
Π142A	Επιτριχέλιο πεπτικό δύοντος	5 997 €	13 1.681 €
Π143A	Μη επιτριχέλιο πεπτικό δύοντος	2 304 €	3 968 €
Π144M	Φλεγμονώδης νόσος του επέρρου με συνιτιδύωσης παθήσεις - επιπλοές	5 997 €	5 577 €
Π144X	Φλεγμονώδης νόσος του επέρρου χωρίς συνιτιδύωσης παθήσεις - επιπλοές	2 563 €	13 2.030 €
Π145M	Απορροή γνωτευτεικού σωλήνη με καταστροφικές (ουσιαστικής ή συναήγορης αυστηρόσυστας παθήσεις - επιπλοές	7 1.217 €	5 891 €
Π145X	Απορροή γνωτευτεικού σωλήνη χωρίς καταστροφικές (ουσιαστικής ή συναήγορης αυστηρόσυστας παθήσεις - επιπλοές	3 569 €	7 1.365 €
Π146A	Καλλινόδη πίνακας ή πατρινό δρός οινούρη	2 327 €	8 1.337 €
Π147M	Οισοσαντρίδα και γαστρεντερίδα με καταστροφικές (ουσιαστικής ή συναήγορης αυστηρόσυστας παθήσεις - επιπλοές	5 933 €	5 891 €
Π147X	Οισοσαντρίδα και γαστρεντερίδα χωρίς καταστροφικές (ουσιαστικής ή συναήγορης αυστηρόσυστας παθήσεις - επιπλοές	2 385 €	7 1.365 €
Π150M	Άλας πεθήσεις του πεπτικού αιγαλούσης με καταστροφικές παθήσεις - επιπλοές	6 1.033 €	2 474 €

ΚΩΔ. ΚΕΝ	ΚΕΝ ΤΕΡΗ ΡΑΦΗ	ΜΔΝ από 1/3/2012	Κέρδος από 1/3/2012
K17M	Ανηκόποτον βιουμασοδοτημένη πηγής με καταστροφικές (ουσιαστικής ή συναήγορης αυστηρόσυστας παθήσεις	5	2.629 €
K17X	Ανηκόποτον βιουμασοδοτημένη πηγής χωρίς καταστροφικές (ουσιαστικής ή συναήγορης αυστηρόσυστας παθήσεις - επιπλοές	1	2.227 €
K18M	Άλας παρθένας για βιουμασότητα σε συνηθισμένη ποσότητα - επιπλοές	7	2.023 €
K18X	Άλας παρθένας για βιουμασότητα σε συνηθισμένη ποσότητα χωρίς πλοκές	2	1.045 €
K19A	Διαδερμικές ενδιογγυατικές καρδιακές επιπλοές	3	2.903 €
K20A	Απολύτων και εκρήσης φλέβων	1	691 €
K21M	Άλεις ρευρούνικης επειδηματικής συνιτιδύωσης παθήσεις-επιπλοές	13	2.187 €
K21X	Άλεις ρευρούνικης επειδηματικής για ποθήρας του κυκλοφορίου χωρίς καταστροφικές (ουσιαστικής αυστηρόσυστας παθήσεις-επιπλοές	4	1.358 €
K22A	Αρσητική βαλβιδοφόρα μογγεύματα	11	7348 €
K30M	Πέθηση του κυκλοφορίου με υψηλούς πυκνοπληκτικούς αντικούς σε κατοπτρικές (ουσιαστικής αυστηρόσυστας παθήσεις-επιπλοές	11	5.401 €
K30X	Πέθηση του κυκλοφορίου με υψηλούς πυκνοπληκτικούς αντικούς χωρίς κατοπτρικές (που σηματίζεται συνηθισμένης παθήσεις-επιπλοές	6	3.649 €
K31M	Διαπορώνες του κυκλοφορίου σε OEM (ορθή φύραγμα μικροφόρου) με επιεμβατικό καρδιακό καθετηριανό πλαστικό με κατοπτρικές (ουσιαστικής αυστηρόσυστας παθήσεις-επιπλοές	8	1.653 €
K31X	Διαπορώνες του κυκλοφορίου σε OEM (ορθή φύραγμα μικροφόρου) με επιεμβατικό καρδιακό χωρίς OEM (ορθή φύραγμα μικροφόρου) με επιεμβατικό καρδιακό καθετηριανό πλαστικό με κατοπτρικές (ουσιαστικής αυστηρόσυστας παθήσεις-επιπλοές	8	1.653 €
K32A	Διαπορώνες του κυκλοφορίου χωρίς OEM (ορθή φύραγμα μικροφόρου) με επιεμβατικό καρδιακό καθετηριανό πλαστικό με κατοπτρικές (ουσιαστικής αυστηρόσυστας παθήσεις-επιπλοές	1	498 €
K32M	Διαπορώνες του κυκλοφορίου χωρίς OEM (ορθή φύραγμα μικροφόρου) με επιεμβατικό καρδιακό καθετηριανό πλαστικό με κατοπτρικές (ουσιαστικής αυστηρόσυστας παθήσεις-επιπλοές	8	1.875 €
K33A	Πέθηση του κυκλοφορίου με μη επιαβατικό σε ποσότητα	13	1.681 €
K33M	Πέθηση της διρφύωσης του κυκλοφορίου με μη επιαβατικό σε ποσότητα (ουσιαστικής αυστηρόσυστας παθήσεις-επιπλοές	8	1.337 €
K33X	Φλεγμονή δρόφων με κατοπτρικό σε ποσότητα	3	968 €
K34M	Δροπιστική έλικη σε διαπορώνες του κυκλοφορίου χωρίς κατοπτρικές (ουσιαστικής αυστηρόσυστας παθήσεις-επιπλοές	5	577 €
K34X	Δροπιστική δρόπη σε διαπορώνες του κυκλοφορίου χωρίς κατοπτρικές (ουσιαστικής αυστηρόσυστας παθήσεις-επιπλοές	13	2.030 €
K35M	Περιφραγή αγγειού παθήσεις-επιπλοές	2	474 €

Major Modelling Assumptions	<p><i>Simplified Markov Cohort in 2 stages: Stage1=6 cycles, Stage2=7-60 cycles (1 cycle = 1 month)</i></p> <p><i>Main cohort events: VTE, MB, CRB, Death</i></p> <p><i>2 CAT Risk Levels: HIGH (CA with Metastasis/Chemo) and LOW (CA no Metastasis/Chemo)</i></p> <p><i>3 Anticoagulant Classes: LMWH, DOAC, and VKA</i></p> <p><i>LMWH vs VKA studies included for HIGH risk population:</i></p> <p><i>CLOT (Dalteparin)¹¹, LITE (Tinzaparin)¹², CATCH (Tinzaparin)¹³, ROMERA2009 (Tinzaparin)²⁹, ONCENOX (Enoxaparin)²⁷, CANTHANOX (Enoxaparin)²⁸</i></p> <p><i>DOAC vs VKA studies included for LOW risk population: AMPLIFY (Apixaban)²⁵, EINSTEIN (Rivaroxaban)²⁴, HOKUSAI (Edoxaban)¹⁸, RECOVER (Dabigatran)²⁶</i></p> <p><i>DOAC vs LMWH studies included for HIGH risk population: HOKUSAI CANCER (Edoxaban) & SELECT-D (Rivaroxaban)¹⁹</i></p> <p><i>LMWH Brands accounted: Enoxaparin (Clexane®), Tinzaparin (Innohep®), Dalteparin (Fragmin®)</i></p> <p><i>DOAC Brands accounted: Rivaroxaban (Xarelto®), Apixaban (Eliquis®), Dabigatran (Pradaxa®), Edoxaban (Lixiana®)</i></p> <p><i>VKA Brands accounted: Warfarin (Sintrom® and Panwarfin®)</i></p> <p><i>Indirect (network) estimation of DOAC Risk Ratios (HIGH risk population) for all event types (VTE, MB, CRB, MOR) vs VKA base, as a simplified product function of available/published RR;</i></p> <ul style="list-style-type: none"> • $RR_{(DOAC \text{ vs } VKA)}^{\text{High Risk CAT}} = RR_{(DOAC \text{ vs } LMWH)}^{\text{High Risk CAT}} \times RR_{(LMWH \text{ vs } VKA)}^{\text{High Risk CAT}}$ <p><i>Disease modelling estimation of LMWH Risk Ratios (LOW risk population) for VTE & MB events vs VKA base as function of average between HIGH risk and non-Cancer available/published RR;</i></p> <ul style="list-style-type: none"> • $RR_{(LMWH \text{ vs } VKA)}^{\text{Low Risk CAT}} = \frac{1}{2} RR_{(LMWH \text{ vs } VKA)}^{\text{High Risk CAT}} + \frac{1}{2} RR_{(LMWH \text{ vs } VKA)}^{\text{non-Cancer VTE}}$ <p><i>LMWH Risk Ratios (LOW risk population) for CRB and MOR events considered equal to those published for DOAC vs VKA in LOW Risk population</i></p> <p><i>Monthly probabilities of VKA base events estimated by exponential distribution of published event rates and LMWH/DOAC probabilities as product of published or modelled RR over the VKA probabilities. Remaining not retrieved LMWH/DOAC probabilities derived by event related (exponential) calculations by available clinical trials</i></p> <p><i>Mortality Probabilities adjusted with additional attributed risk by fatal bleeding after the incidence of a MB or fatal PE after the incidence of recurrent PE⁸</i></p> <ul style="list-style-type: none"> • $P_{\text{Total Mortality}} = P_{\text{CA Mortality}} + (P_{\text{VTE death}} * P_{\text{VTE event}}) + (P_{\text{MB death}} * P_{\text{MB event}}) \rightarrow$ • $P_{\text{Total Mortality}} = P_{\text{CA Mortality}} + (1 - e^{-0.17}) * P_{\text{VTE event}} + (1 - e^{-0.28}) * P_{\text{MB event}}$ <p><i>VTE/MB/CRB events ceased after 6 months with stage 2 (7-60months) probabilities accounting only CA related mortality.</i></p> <p><i>Utility estimation based on 60 months (stage 2) projected cohort events (per risk level) adjusted by utility per event type. MB/VTE/CRB utilities estimated to resolve within 6 month period.</i></p> <p><i>CAT utility per event type⁷: Entry (no event)= 0.645, MB=0.593, VTE=0.570, CRB=0.622</i></p>
Major Cost Assumptions	<p><i>Inclusion of direct pharmacological costs for secondary thromboprophylaxis (as average per class)</i></p> <p><i>All drug costs at hospital level prices; retrieved in the Greek Healthcare setting (Gallinos.gr)³⁰⁻³⁷</i></p> <p><i>5 days of LMWH lead in requirement in line with SmPC dosing of different anticoagulant agents (Pradaxa® & Lixiana®)^{34,36}</i></p> <p><i>Average patient weight of 75kg</i></p> <p><i>Inclusion of secondary support costs of VKA treatment (INR laboratory testing and HCP consultation visits)</i></p> <p><i>15 INR tests and 8 HCP visits over the 6 months period accounted with decreasing frequency pattern. INR and HCP costs according official government price gazette³⁸</i></p> <p><i>Diagnosis Related Group (DRG) recorded cost in the Greek health system for the management of VTE, MB and CRB events (official government price gazette)³⁹</i></p> <p><i>Mortality and other Indirect costs: Not accounted</i></p>

Table H: Summary of Modelling and Cost assumptions of the analysis.