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Are direct oral anticoagulants an economically attractive alternative to low molecular weight heparins in lung cancer associated venous thromboembolism management?

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Abstract
Venous thromboembolism is highly prevalent in lung cancer patients. Low molecular weight heparins are recommended for long term treatment of cancer associated venous thromboembolism. Direct oral anticoagulants are however an interesting alternative as they are administered orally and don't require monitoring. There are currently studies comparing both their efficacy and tolerance for cancer patients and more and more guidelines suggest considering direct oral anticoagulants for cancer associated venous thromboembolism treatment. The objective of this study was to evaluate the budgetary impact that direct oral anticoagulants use would have for lung cancer associated venous thromboembolism treatment and prevention in France. An economic model was made to evaluate the cost of venous thromboembolism treatment and prevention among patients with primary lung cancer in France by two strategies: current guidelines versus direct oral anticoagulants use. The model was fed with clinical and economic data extracted from the French national health information system. The analysis was conducted from the national mandatory Health insurance point of view. The time horizon of the study was the evaluation of the annual management cost. Lung cancer associated venous thromboembolism management's mean cost was estimated of 836€ per patient, that is a total cost of about 40 million euros per year at a national level. A 76% decrease of this cost can be expected with direct oral anticoagulants use. However, despite their benefits, these treatments raise new issues (medication interactions, bleeding management), and would likely not be recommended for all patients.

Keywords Lung cancer · Venous thromboembolism · Anticoagulant therapy · Direct oral anticoagulant · Economic impact

Highlights

- Direct oral anticoagulants are an attractive alternative to low molecular weight heparins.
- Lung cancer associated venous thromboembolism's costs were estimated at 836€ per patient.
- A decrease up to 76% of this cost can be expected with direct oral anticoagulant use.

Introduction

Venous thromboembolism (VTE), which includes both deep vein thrombosis (DVT) and pulmonary embolism (PE), is a frequent disease among patients with lung cancer, more than 8% of patients experience VTE during the year following cancer diagnosis in France according to our previous work [1]. Lung cancer is the most frequent cancer localization in

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France, 49,000 incident cases were estimated in 2017 [2]. Lung cancer prognosis is poor with a 5-year median survival time of only 17% [2].

Cancer is a major VTE risk factor; especially during the month following cancer diagnosis [3], 15 to 20% of all VTE events are associated with cancer [4]. This risk is due to cancer itself as well as to the exposure to some thrombogenic factors such as surgery, trauma, and immobilization [5]. There are specific recommendations for cancer associated VTE treatment and prevention [6], which are demanding for patients and require many healthcare resources [7]. Low molecular weight heparin injections (LMWH), with a curative dose, are recommended for 7 to 10 days as initial treatment. Unlike for non-cancer associated VTE, this treatment should be continued for 3 to 6 months. Treatment can then be stopped if it was the first VTE event and if the cancer is non-evolutive and untreated, otherwise anticoagulation must be continued, and it can be switched to an oral therapy with a vitamin K antagonist (VKA) or a direct oral anticoagulant (DOAC).

Heparins are also recommended as primary prophylaxis for cancer associated VTE during hospitalization. In the context of oncologic surgery, prophylaxis is also recommended for at least 7 to 10 days and can be continued for 4 weeks. Prevention with a LMWH is suggested to be considered during the course of chemotherapy, in regards of the bleeding risk, when lung cancer is locally advanced or metastatic [6, 8].

DOACs are an attractive treatment compared to LMWHs as they are administered orally and not injected subcutaneously, and they don't require any monitoring. They are currently not recommended for cancer associated VTE treatment [8, 9], but if they proved to be as effective and well tolerated as LMWHs, they could improve the patient's care and quality of life. More and more guidelines suggest considering them for patients with a stable cancer who are not under chemotherapy and when VKAs are not an option. A careful selection of eligible patients must be performed [10, 11]. Guidelines on PE management have been recently updated and recommend to consider using edoxaban or rivaroxaban as an alternative to LMWHs for cancer patients except in case of gastrointestinal cancer [12].

DOACs are a well-established interesting alternative to VKAs in VTE treatment for non-cancer patients. Some meta-analyses conducted on cancer subgroups in randomized clinical trials suggest they are also non inferior to VKAs for cancer associated VTE treatment [13]. However, VKAs are not the standard treatment for these patients and there is scarce data comparing DOACs to long term treatment with LMWHs in terms of tolerance and efficacy. Studies evaluating DOACs in cancer associated VTE are currently emerging with promising results in terms of efficacy, but a concern remains regarding the bleeding risk [14].

Some authors suggest that LMWHs could be switched to DOACs for some patients, especially for those with stable cancer under oral chemotherapy, maintenance intravenous chemotherapy, after immunotherapy or if they have a long life-expectancy. The switch should then be made according to the patients' wishes in regards of medication interactions and renal and hepatic functions [7].

Cancer associated VTE treatment is not easy as it must balance the bleeding risk induced by anticoagulants in a population already at high risk. New studies emerging are questioning the current guidelines by evaluating the use of DOACs, which are of simpler use [15]. The results of these studies could have great impact for cancer patients' care. As cancer associated VTE is a frequent disease, we wonder what the economic impact of such a change in the current guidelines would be.

The primary objective of this study was to evaluate the preventive and curative cost of VTE management for patients with lung cancer in France according to the current guidelines and to model the economic impact of DOAC use. The secondary objective was to describe the evolution of DOAC's prescriptions frequencies for these patients.

Methods

Budgetary impact evaluation

Economic model

An economic model was computerized with Microsoft Excel (Microsoft Corp, Remond, WA) to evaluate the cost of VTE treatment and prevention among patients with primary lung cancer in France by two strategies: current guidelines versus DOAC use. French health authority and economic society guidelines for economic analyses were followed [16, 17]. The model was fed with clinical and economic data for both scenarios in order to evaluate the budgetary impact of DOAC use. The analysis was conducted from the national mandatory Health insurance point of view. The time horizon of the study was the evaluation of the annual management cost.

Population, clinical and therapeutic data

Data from a national epidemiological study conducted with an insurance claims database, the *échantillon généraliste des bénéficiaires* (EGB) was used to model the natural course of the disease and its management. The EGB is an anonymous permanent random sample (1/97th), extracted from the total population database recorded by the French mandatory Health insurance system, which is representative of

this population. The data is made available to accredited researchers and contains individual, exhaustive and linkable but anonymous data [18]:

- Patients' characteristics such as sex, age, date of birth and death;
- French Diagnosis-Related Group prospective payment system which collects main and associated diagnoses encoded using the International Classification of Diseases 10th revision (ICD-10), and procedures performed during hospital stays (in all public and private hospitals), using the French common classification system for medical procedures (CCAM);
- the reimbursement data for out-of-hospital care (consultations, procedures, drugs);
- the codes for long-term illnesses (ALD), which provide patient coverage.

Various control procedures are regularly conducted to ensure the quality of these data. The reliability of the French Health insurance system database, has been established in recent studies [19], including ours, initially including only the hospital database but more recently the whole database [20–26].

The model evaluates the annual management cost for the 49,000 patients diagnosed with primary lung cancer each year in France (2017 incidence [2]). The first therapeutic strategy is in accordance with current guidelines. The second therapeutic strategy introduces the possible use of DOACs. Both therapeutic strategies are detailed in Fig. 1.

For both strategies:

- The number of patients to treat for a VTE is estimated with the proportion of patients who presented VTE in the EGB-based epidemiologic study, including VTE diagnosed concomitantly with cancer diagnosis, that is 9.5%. Among these patients, the number of patients with renal insufficiency is also estimated with the proportion found in the EGB-based study, that is 3.5%. A total treatment duration of 6 months was chosen for the

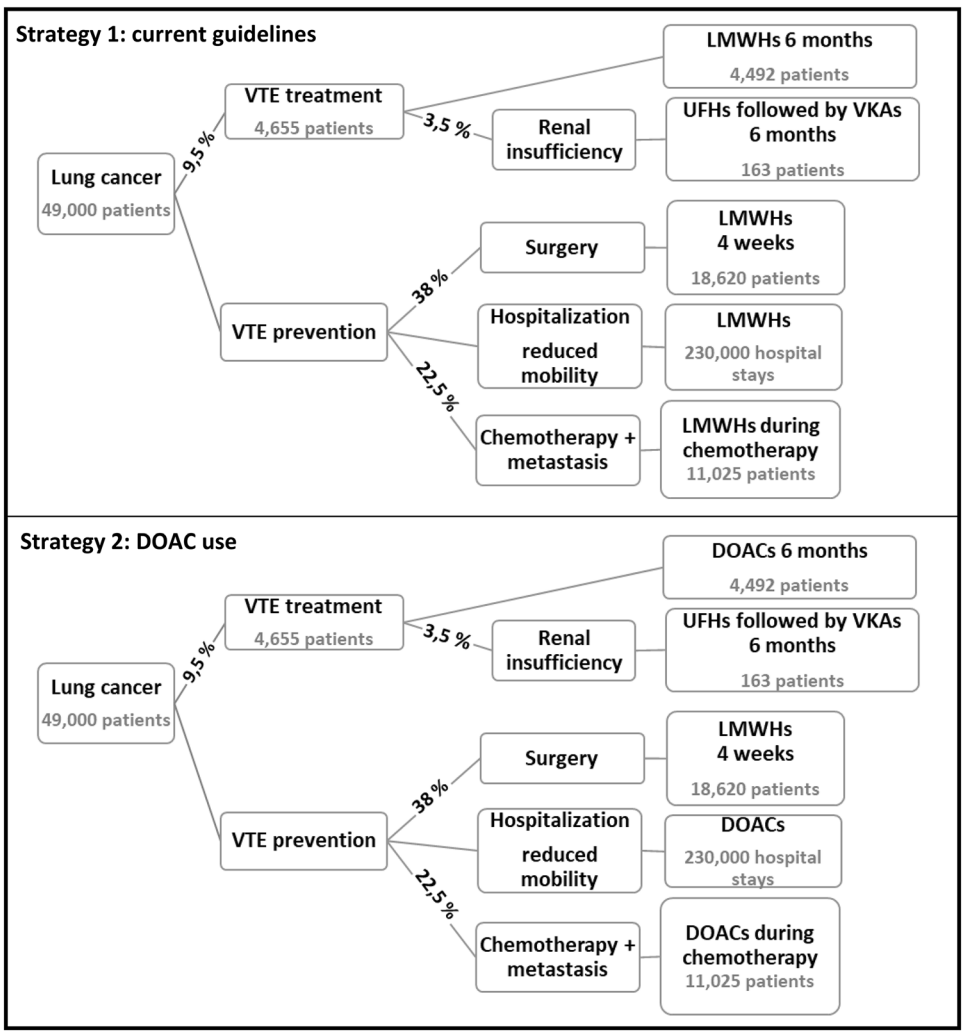

Fig. 1 Strategies compared for preventive and curative management of lung cancer associated VTE

primary analysis. A ten days long initial treatment with heparin was defined when followed with VKAs with an eight days long overlapping period. Hospitalization was defined to last seven days as it is the mean duration of hospital stays for lung cancer patients in France [27]. For the second strategy with DOAC use, the primary analysis was conducted for an initial VTE treatment with DOAC for patients with normal renal function.

– The number of patients eligible for pharmacological VTE prevention was assessed according to the proportion of patients undergoing surgery or chemotherapy for a metastatic cancer found in the EGB-based study, that is respectively 38% and 45%. For chemotherapy, this proportion was weighted with the proportion of patients at high thrombotic risk (estimated of 45% according the CANTARISK study [28]), a final proportion of 22.5% was therefore defined for chemotherapy eligible patients. The duration of preventive anticoagulation was defined of 90 days for chemotherapy as protocols are made of at least 4 cycles of 21 days [29, 30]. For surgery associated prevention, a 4-week anticoagulation was defined for the primary analysis, with a 12-day hospital stay after surgery, according to the mean length of stay for respiratory cancer surgeries [27]. The annual number of hospitalizations for lung cancer patients—excluding surgical stays—is estimated of 230,000, with a 7-day long mean length of stay [27].

Costs

Medication and medication-associated resources (administration, biological monitoring) were identified and measured for each scenario. The place of medication administration (hospital or ambulatory) was considered for the costs calculation as the individual costs are different for medication as well as nurse time. All resources were priced according to national fixed prices for medication and medical acts. The pricing is detailed in Table 1.

The LMWH chosen for VTE treatment was tinzaparin as it has a marketing authorization for long-term use in cancer patients and it can be administered once a day, which fits to ambulatory use. The LMWH chosen for VTE prevention was enoxaparin as it is the most used LMWH for prevention in France [31]. As apixaban and rivaroxaban have very similar daily costs, their mean costs were used for DOAC VTE treatment and prevention.

LMWH administration was estimated to take a nurse five minutes. Biological monitoring frequency was determined according to guidelines [36]. For a 6-month long LMWH VTE treatment, 13 platelet counts were defined (10 for a 3-month treatment, 4 for a 10-day one and 8 for 4-week one). Platelet counts were not factored in for preventive anticoagulation associated with chemotherapy as we considered blood counts were checked regardless of anticoagulation. For INR (International Normalized Ratio) monitoring, 9 acts were defined for a 3-month VKA treatment and 13 for a 6-month one. Two measure of the Anti-Xa activity were defined for a 10-day treatment with unfractionated heparins (UFH).

Results presentation

The mean annual cost of treatment and/or prevention of VTE was presented for each strategy. The cost associated with each situation was detailed while distinguishing the

Table 1 Unitary costs of resources necessary for treatment and prevention of VTE

	Unitary costs	Reference
Biological monitoring		
Platelet count	4,05€	CNAMTS-medical biology acts nomenclature (Code B15) [32]
INR	5,40€	CNAMTS-medical biology acts nomenclature (Code B20) [32]
Anti-Xa activity	8,10€	CNAMTS-medical biology acts nomenclature (Code B30) [32]
Nurse		
In hospital care (5 min)	1.30€	Nurses' mean monthly income (2,324€ [33]) for 35 h per week
In ambulatory care	7,23€	Ameli-Professional acts general nomenclature [34]: subcutaneous injection for cancer patients (1,5 AMI = 4,73€) + traveling fee (1 IFD = 2,50€)
Medications (daily costs in ambulatory/hospital)		
UFH: calcium heparin	3,30€/2.45€	SPC[2] Calciparine®, 2 injections per day
Curative LMWH: Tinzaparin	13,70€/1.23€	SPC Innohep®
Preventive LMWH: Enoxaparin	6,19€/0.66€	SPC Lovenox®
DOAC: Apixaban, Rivaroxaban	2,18€/0.35€	SPC Eliquis®, 2 intakes per day or Xarelto®, 1 intake per day
VKA	0,13€	*De Pouvourville* et al. [35]

INR International Normalized Ratio, *SPC* summary of product characteristics

medication, administration and monitoring costs. The cost differences per patients according to each strategy were presented. The annual budgetary impact of DOAC use was also estimated at a national level for all patients diagnosed with primary lung cancer each year in France.

Univariate sensitivity analyses with the base case analysis were made with four alternative scenarios to study the impact of:

- Reducing VTE treatment from 6 to 3 months;
- Reducing preventive anticoagulation associated with surgery from 4 weeks to 10 days;
- An initial treatment with LMWH for 10 days before using DOACs instead of an initial treatment with DOAC for the DOAC strategy;
- A − 30% variation of enoxaparin's price (in prospect of biosimilars marketing authorization).

Description of the frequency of DOAC prescription

DOAC deliveries were searched in the EGB for all active lung cancer on the one hand and for all active cancers on the other hand from 2012 to 2016. Patients were considered to have an active cancer if they had during the 2 years prior to a DOAC delivery: an ALD initiation for cancer or a hospitalization with diagnosis codes for chemotherapy, radiotherapy or metastasis, or deliveries of oral targeted cancer therapies. The method for active lung cancer patient's identification was previously validated [37]. Deliveries of rivaroxaban, apixaban and dabigatran were differentiated. For each year, the proportion of patients with at least one DOAC delivery over the year among the patients identified as having an active cancer is presented, globally and for each DOAC.

Regulatory aspects

Written consent was not needed for this non-interventional retrospective observational study. The EGB database use was approved by the French national data protection agency (CNIL). Therefore, this study was conducted in accordance with the Declaration of Helsinki.

Results

Costs estimation and budgetary impact analysis

The mean annual cost of treatment and/or prevention of lung cancer associated VTE in France is estimated of 836€ with current guidelines and of 203€ with the second strategy using DOACs, that is a 76% reduction of costs with the second strategy. The costs of treatment and prevention of VTE are detailed in Table 2.

Table 2 Individual costs of curative and preventive anticoagulation for lung cancer associated VTE in France

	Costs per patient and per event (€)		
	Strategy 1: current guidelines	Strategy 2: DOACs	Difference (€)
Curative treatment			
No severe renal insufficiency			
Medication cost	2329	379	− 1950
Administration cost	1259	0	− 1259
Monitoring cost	53	0	− 53
Total	3641	379	− 3262
Severe renal insufficiency			
Medication cost	48	48	–
Administration cost	103	103	–
Monitoring cost	13	13	–
Total	164	164	–
Preventive treatment			
Surgery			
Medication cost	117	117	–
Administration cost	145	145	–
Monitoring cost	32	32	–
Total	294	294	–
Hospitalization			
Medication cost	5	2	− 3
Administration cost	9	0	− 9
Monitoring cost	12	0	− 12
Total	26	2	− 24
Chemotherapy			
Medication cost	545	196	− 349
Administration cost	650	0	− 650
Total	1195	196	− 999

The total annual costs were estimated of 40,968,155€ for the current guidelines and of about 9,947,855€ for the DOAC strategy as detailed in Table 3.

The alternative scenarios results (univariate sensitivity analyses with the primary analysis) are presented in Table 4. The strategy with DOACs results in a 72 to 86% decrease of the mean cost per patient of lung cancer associated VTE management according to the different alternative scenarios.

The extrapolated annual costs of curative and preventive anticoagulation for lung cancer associated VTE in France according the different sensitivity analysis scenarios are presented in Tables 5 and 6. The total annual cost for preventive anticoagulation is estimated of about 8,000,000€ according to current guidelines for a minimal 3-months treatment. If VTE was treated with DOACs following an initial treatment with LMWHs, the annual cost would amount to 1,300,000€ for a 3-months treatment and to 2,000,000€ for a 6-months treatment. Preventive anticoagulation is estimated of 650,000€ for a minimal 10-days treatment following surgery.

Table 3 National annual budgetary impact of DOAC use for lung cancer associated VTE management: base case analysis

	Total annual cost (€)		Difference (€)
	Strategy 1: current guidelines	Strategy 2: DOACs	
Curative treatment			
No severe renal insufficiency (N = 4492)	16,351,242	1,711,755	14,639,487 (−89%)
Severe renal insufficiency (N = 163)	26,559	26,559	–
Preventive treatment			
Surgery (N = 18,620)	5,489,490	5,489,490	–
Hospitalization (N = 230,000)	5,918,823	5,58,895	5,359,928 (−91%)
Chemotherapy (N = 11,025)	13,182,041	2,161,156	11,020,885 (−84%)
Total	40,968,155	9,947,855	31,020,300 (−76%)

Table 4 Mean costs per patient of lung cancer associated VTE management according to alternative scenarios

	Strategy 1: current guidelines		Strategy 2: DOACs		Difference between strategy 1 and 2 (€)
	Mean cost per patient (€)	Variation in comparison of the primary analysis	Mean cost per patient (€)	Variation in comparison of the primary analysis	
Base case analysis	836	–	203	–	633 (−76%)
Alternative scenario 1: *3-months curative treatment*	665	−21%	185	−9%	480 (−72%)
Alternative scenario 2: *10-days surgical prevention*	738	−12%	105	−49%	633 (−86%)
Alternative scenario 3: *Curative treatment with DOAC following an initial treatment with LMWH (strategy 2)*	836	–	212	+4%	624 (−75%)
Alternative scenario 4: *Enoxaparin's price* − 30%	788	−6%	198	−2%	590 (−75%)

Table 5 National annual costs of curative anticoagulation for lung cancer associated VTE according to alternative scenarios

N = 4655	Strategy 1: current guidelines		Strategy 2: DOACs		Difference between strategy 1 and 2 (€)
	Total cost (€)	Variation in comparison of the primary analysis	Total cost (€)	Variation in comparison of the primary analysis	
Base case analysis	16,377,801	–	1,738,314	–	14,639,487 (−89%)
LMWH vs LMWH followed by DOAC 6 months	16,377,801	–	2,202,264	+27%	14,175,537 (−87%)
LMWH 3 months	7,975,340	−51%	852,338	−51%	7,123,002 (−89%)
LMWH vs Relais LMWH followed by DOAC 3 months	7,975,340	−51%	1,316,288	−24%	6,659,052 (−83%)

If enoxaparin had a 30% lower price, the decrease observed for the DOAC strategy would remain in the same order of magnitude.

Evolution of DOAC use

Among patients with active lung cancer, 5.7% were treated with DOACs in 2016, regardless of indication (1.7% with apixaban, 3.4% with rivaroxaban and 0.6% with dabigatran). These figures are slightly lower than for all cancer, where 7.5% of patients were treated with DOACs (2.6% with

Table 6 National annual costs of preventive anticoagulation for lung cancer associated VTE according to alternative scenarios

Prevention situation	Strategy 1: current guidelines		Strategy 2: DOACs		Difference between strategy 1 and 2 (€)
	Total cost (€)	Variation in comparison of the primary analysis	Total cost (€)	Variation in comparison of the primary analysis	
Surgery (N = 18,620)					
Primary analysis	5,489,490	–			0
Enoxaparin's price – 30%	5,262,715	– 4%	Likewise strategy 1		0
LMWH 10 days	662,979	– 88%			0
LMWH 10 days + *Enoxaparin's price* – *30%*	625,907	– 89%			0
Hospitalization (N = 230,000)					
Primary analysis	5,918,823	–	5,58,895	–	5,359,928 (– 91%)
Enoxaparin's price – 30%	5,598,280	– 5%	5,58,895	–	5,039,395 (– 90%)
Chemotherapy (N = 11,025)					
Primary analysis	13,182,041	–	2,161,156	–	11,020,885 (– 84%)
Enoxaparin's price – 30%	11,378,131	– 14%	2,161,156	–	9,216,975 (– 81%)

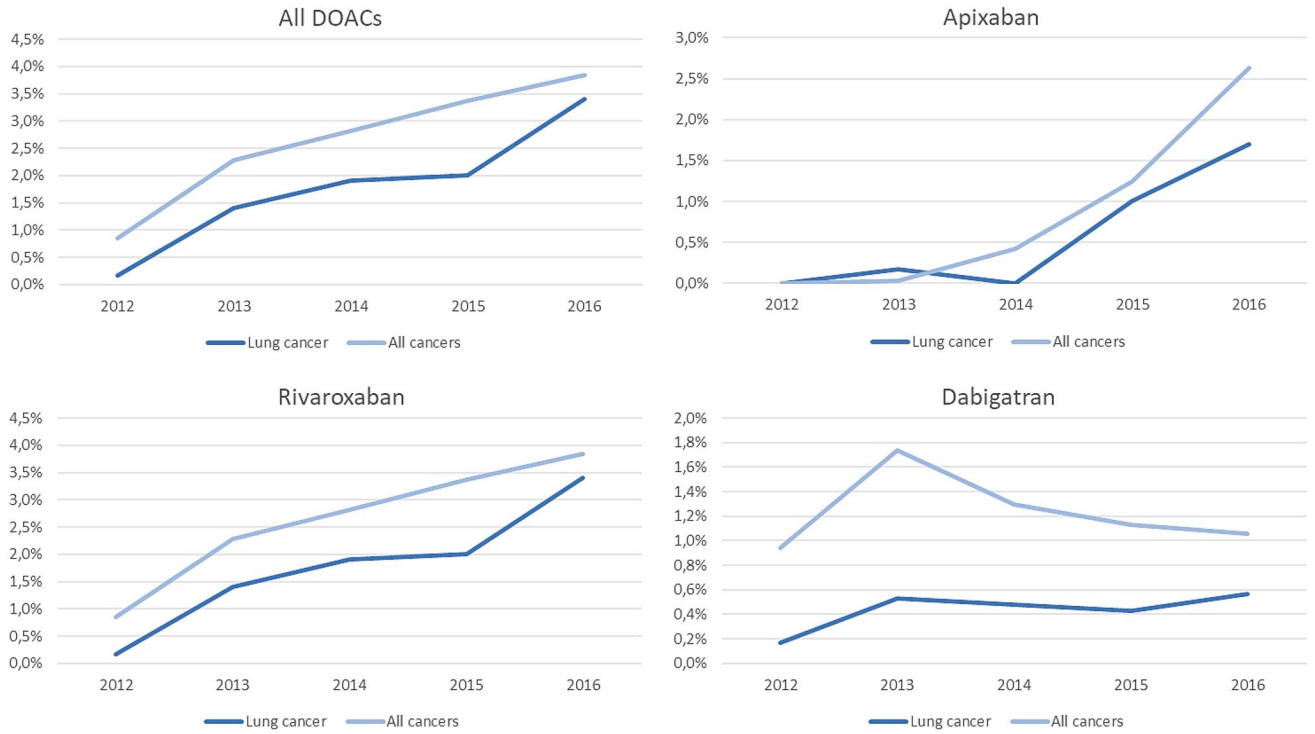

Fig. 2 Proportions of patients receiving a DOAC treatment among patient with active cancer

apixaban, 3.8% with rivaroxaban and 1.1% with dabigatran). The evolution of prescriptions since DOACs' marketing authorization is detailed in Fig. 2.

Discussion

Costs estimation and budgetary impact analysis

The annual cost of curative and preventive anticoagulation for lung cancer associated VTE in France is quite substantial, as a total of 40 million euros was estimated while only

accounting for the 1-year period following cancer diagnosis, that is an 800€ annual cost per patient. Anticoagulation prevention represents more than half of the cost.

Beyond the lower burden of DOACs *versus* LMWHs as a long-term treatment for lung cancer associated VTE management, this strategy could result in a significant cost reduction, about 75%, which could also be extended to other cancer localizations. It is interesting to notice that this reduction would remain significant with a reduction of enoxaparin's price, as is expected with the marketing authorizations for biosimilars. Indeed, the difference in costs observed between both strategies is not only related to the difference between DOACs and LMWH's prices but it is also associated with the cost of administration by a nurse and biological monitoring which are not necessary with DOACs. However, the budgetary impact evaluation considered a switch to DOACs for all patients, which is quite unlikely as they have a few downsides. Indeed, there can be pharmacological interactions between DOACs and other medications using the same metabolic pathways, especially oral targeted anticancer therapies which are used for some lung cancer treatment. Moreover, chemotherapy induced emesis can lead to a reduced absorption of DOACs and lessen their effectiveness. DOAC's effects are also unpredictable if renal and hepatic functions are altered or in case of malnutrition leading to a lower fixation to plasmatic proteins. To guaranty the effectiveness of DOAC treatment, patient's compliance is essential as they are responsible for their own treatment unlike for LMWHs which are administered with a nurse's help. Lastly, for patients with a high bleeding risk, DOACs are not a prudent choice as they cannot be monitored, and no antidote is yet available (except for dabigatran).

One of the major strengths of this economic evaluation is it was based on real life data observed with the EGB and extrapolated to all incident cases in France. Moreover, the hospital and ambulatory costs were differentiated in order not to overestimate the total management costs. Indeed, medication prices are fixed at a national level in the ambulatory setting, but hospitals can negotiate those prices which can lead to considerable reductions. The cost for nurse time is also more important at home than in hospitals. The results of this study are very relevant on a clinical point of view as they show that if DOAC use is considered and approved for lung cancer patients, economic matters are not an issue. This study could bring elements to the French economic comities that decide on the reimbursement by the health insurance system for these patients.

The limits of this economic evaluation are that the durations of anticoagulation modelized were based on the guidelines, but they can differ in real life. Indeed, the duration can be shortened if the patients died before ending the treatment or if it was discontinued for some reason; on the contrary the treatment can also be prolonged over 6 months. Preventive anticoagulation was considered during the course of chemotherapy in this analysis, however only some guidelines suggest considering anticoagulation for these patients and only for patients with a favorable benefit-risk balance in regards of bleeding and thrombotic risks, this balance could not be modelized with the data available. Lastly, the branches of the model may sometimes overlap as a situation where prevention is to be considered may be at the same time as an effective VTE to treat or another prevention situation, costs may then not be added.

Moreover, we considered a health insurance point of view for this analysis, but other factors could have an influence on costs, such as return to work issues or treatment complications. We considered including the return to work issue in the model, but we didn't find any relevant difference between the two strategies concerning this issue. However, the issue of treatment complications could be very relevant. Modeling the costs of bleeding management with both LMWHs and DOACs would have been interesting. An algorithm to identify patients eligible to a DOAC treatment would allow to improve this budgetary impact analysis.

Vena cava filters are a therapeutic option for severe PE when anticoagulants are contra-indicated. This was not modelized as no reliable data on their frequency of use was available and we considered it marginal given the national usage data for vena cava filters (27). The cost of venous contention was not accounted for either. As for biological monitoring and nurses' acts, supplements were not accounted for. All of this probably leads to an underestimation of the real cost of VTE management.

Lastly, this economic model as presented only applies to the French healthcare system. Depending on the country's healthcare system and initial VTE treatment strategy, scalability and applicability to other countries may vary. That's why we performed a sensitivity analysis with four alternative scenarios, including costs and treatment strategy variation. Our results are, however, robust (ranging from − 72 to − 86% between strategy 1 and 2). Although, this could be transposed to other countries in further studies.

Evolution of DOAC use

Since DOACs have been a therapeutic option for VTE prevention and treatment, there has been a constant increase in their use even among cancer patients, except for dabigatran. DOACs are less frequently used among lung cancer patients than among all cancer patients. As DOACs can be used for VTE prevention for patients with atrial fibrillation even for patients with cancer, this may simply reflect that lung cancer is one of cancer localizations with the most important VTE risk and that more patients are anticoagulated with LMWHs and not oral anticoagulants.

Conclusion

This is the first study estimating the cost of curative and preventive anticoagulation for lung cancer associated VTE in France and evaluating the budgetary impact of DOACs use instead of LMWHs. According to current guidelines, we estimated the mean cost of 836€ per patient, that is a total cost of 40 million euros annually at a national level. A reduction of 76% of this cost can be expected with DOACs use. Despite their benefits (ease of administration and monitoring), these anticoagulants expose to other issues (pharmacological interactions, lack of specific antidote for all DOACs) and would not be the best choice for all patients, but they would offer an economically attractive alternative if they proved as effective and well tolerated as LMWHs.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest relevant to this article to disclose.

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