

Direct oral anticoagulants versus low-molecular-weight heparins for venous thromboembolism prevention following total knee replacement: comparative effectiveness and medical costs from a french nationwide cohort study of around 60,000 patients

P Blin ¹, CM Samama ², A Sautet ³, P Mismetti ⁴, J Benichou ⁵, S Lignot-Maleyran ¹, S Lamarque ¹, S Lorrain ¹, R Lassalle ¹, AF Gaudin⁶, FE Cotte⁶, C Droz-Perroteau ¹ and N Moore ^{1,7,8}

¹ Bordeaux PharmacoEpi, Inserm CIC Bordeaux CIC1401, Bordeaux, France – ² Cochin hospital, Paris, France – ³ Saint Antoine hospital, Paris, France – ⁴ Saint Etienne University Hospital, Saint Etienne, France – ⁵ Rouen University Hospital, Rouen, France – ⁶ Bristol-Myers Squibb, Rueil-Malmaison, France – ⁷ Bordeaux University Hospital, Bordeaux, France – ⁸ INSERM U1219, Bordeaux, France

Background

Eliquis® (apixaban) is an antithrombotic agent that directly inhibits factor Xa, and which has obtained market authorization in the indication “Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery (THR or TKR)”.

The French health authorities (Transparency Commission) gave positive approval to the reimbursement of Eliquis® in this indication and requested a follow-up cohort study of patients treated in France by Eliquis® under real-life condition to describe characteristics of treated patients, use, frequency of clinical VTE event occurrence, safety in terms of major bleeding and impact on the healthcare system. Furthermore, the demand specified that Eliquis® had to be compared to usual care under real-life conditions.

Disclosure statement

This study was supported by an unrestricted grant from Bristol-Myers Squibb and Pfizer. It was designed, conducted, and analysed independently by the Bordeaux PharmacoEpi of the Bordeaux University. It was overseen by independent experts.

Objectives

The aim of the study was to assess effectiveness, risk and medical costs of Direct Oral Anticoagulants (DOAC) *versus* Low-Molecular-Weight Heparin (LMWH) for venous thromboembolism (VTE) prophylaxis following total knee replacement (TKR) in real-life setting, with a focus on apixaban.

Methods

Study design

- Cohort study in the SNDS nationwide claims database including all patients with TKR in France between 2013 Jan-1st and 2014 Sept-30th, three-year database history, home return after discharge, DOAC (apixaban, dabigatran, rivaroxaban) or LMWH dispensing within one week after discharge, and followed up for 3 months after discharged.
- DOAC were 1:1 matched on gender, age and propensity score with patients receiving LMWH.

Data source

SNDS database contains individual pseudonymised information on:

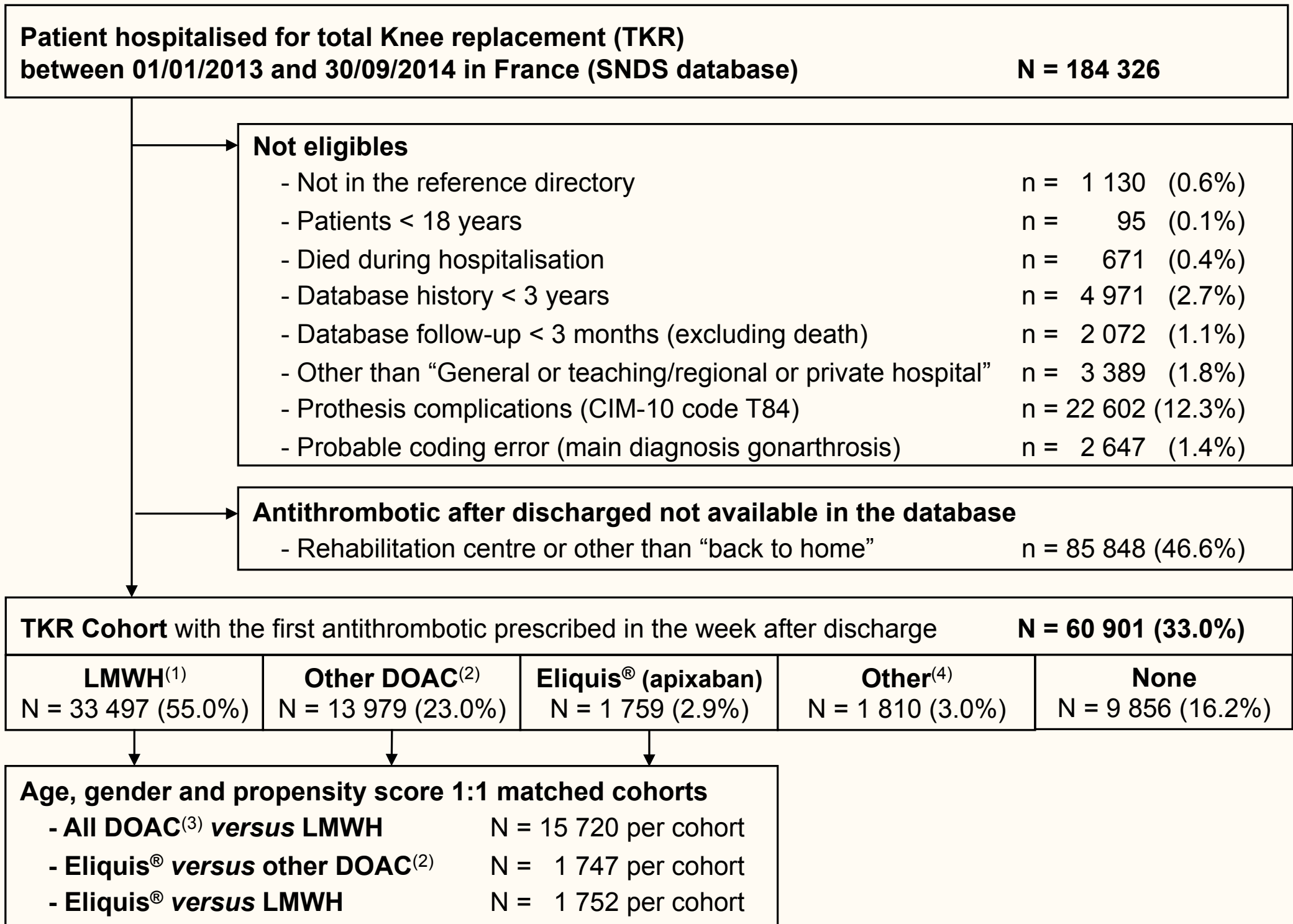
- Gender, date of birth, indicator of low income area of residence, date of death;
- Long-term disease (LTD) registration with associated ICD-10 codes for full insurance coverage (with start and end dates);
- Outpatient reimbursed healthcare expenditures with codes, cost, date of event and date of prescription, prescriber and professional caregiver information;
- Hospital discharge summaries with ICD-10 codes for primary and associated diagnosis, and linked diagnosis for ICD-10 Z-codes (e.g. chemotherapy), for all private and public medical, obstetric and surgery hospitalizations, with the date and duration of hospitalization, medical procedures, DRG cost coding system, and expensive drugs which do not include anticoagulant.

Data analysis

- Relative risk (RR) of hospitalized VTE and bleeding during drug exposure were estimated using quasi Poisson model.
- Medical costs were calculated in euros (€) according the societal perspective for the same period using diagnosis related group for hospitalisations and claims reimbursement for outpatient healthcare resources.

Results

- Among the 60,901 patients hospitalised with a diagnosis of TKR between 2013 Jan-1st and 2014 Sept-30th, and with the 1st antithrombotic prescribed in the week after discharge (not eligible patients excluded):
 - 15,738 were treated with a DOAC in the week after discharge (Figure 1) and 1,759 with apixaban;
 - 33,497 were treated with LMWH;
 - ≥ 95 % of dispensations the day or the day after discharge.



(1) Low Molecular Weight Heparin (2) Dabigatran or rivaroxaban (3) Apixaban, dabigatran or rivaroxaban (4) Unfractionated heparin, fondaparinux, VKA (n=1217 (2.0%)) or antithrombotic association (n=593 (1.0%)).

Figure 1: Population flow chart

- Characteristics of patients are presented in Table 1.
- Nearly all cohort DOAC patients included have been individually matched to a LMWH patient, 15,720 patients by cohort.

Results

Table 1: Description of patients treated with DOAC and patients treated with LMWH

	All patients		Matched patients		Standardized differences, %		
	DOAC n = 15 738	LMWH n = 33 497	DOAC n = 15 720	LMWH n = 15 720	Crude	Adjusted	Matched
Male, %	47.1	47.0	47.1	47.1	0.2	-0.3	0.0
Age, mean (standard deviation)	67.6 (8.9)	68.5 (9.5)	67.6 (8.9)	67.6 (8.9)	10.2	-0.6	0.0
IMPROVE VTE risk score ⁽¹⁾ , %					5.7	-0.5	-2.1
1	20.0	18.1	19.9	19.9			
2	70.5	71.2	70.6	71.3			
>3	9.5	10.6	9.5	8.7			
IMPROVE bleeding risk score ⁽¹⁾ , %					2.7	-0.1	-0.4
< 2	18.6	18.1	18.6	18.3			
2 – 3.5	48.3	48.2	48.3	48.7			
4 – 6.5	32.5	32.9	32.6	32.6			
≥ 7	0.6	0.9	0.6	0.4			
Individual VTE or bleeding risk factors							
- Cancer history, %	12.1	12.9	12.1	10.8	2.5	0.0	-4.2
- Active cancer ⁽²⁾ , %	8.8	9.6	8.8	8.1	2.7	0.1	-2.5
- Atrial fibrillation, %	3.9	5.5	3.9	3.1	7.8	2.7	-4.0
- Rheumatic disease, %	1.1	1.2	1.1	0.9	0.3	-0.1	-1.9
- Recent antithrombotic treatment history ⁽³⁾ , %	19.6	27.4	19.5	19.1	18.5	3.6	-1.0
- Oral contraception or HRT ⁽⁴⁾ , %	10.5	10.1	10.5	9.9	-1.5	-0.1	-1.9
- Antiplatelet agent ⁽⁵⁾ in the week after discharge, %	2.0	3.4	2.0	1.9	8.8	3.9	-0.5
- ASA ⁽⁶⁾ during follow-up, %	1.2	1.1	1.2	0.8	-0.9	0.5	-4.2
TKR index hospitalisation							
- Category of hospital, %							
Teaching hospital	8.1	7.9	8.1	6.9	-0.7	0.6	-4.6
Other public hospital	10.5	16.6	10.5	11.0	17.7	5.9	1.8
Private hospital	81.4	75.5	81.5	82.1	-14.2	-0.8	1.7
- Duration, mean (standard deviation)	7.7 (2.3)	8.0 (3.1)	7.7 (2.3)	7.7 (2.4)	12.5	0.9	1.5
- Hip, pelvis or leg fracture, %	0.3	1.4	0.3	0.2	-	-	-
- Bleeding diagnosis during hospitalisation, %	1.8	2.6	1.8	1.6	5.1	0.9	-1.3
Treatment duration ⁽⁷⁾ (days), mean (standard deviation)	29.1 (6.9)	25.6 (8.4)	29.1 (6.9)	25.6 (8.3)	-	-	-

(1) Mean standardised difference; (2) Treatment on-going within the year before TKR; (3) Within 3 month before TKR; (4) Hormone Replacement Therapy; (5) Acetylsalicylic acid, clopidogrel, prasugrel or ticagrelor; (6) Acetylsalicylic acid; (7) Estimated from number of units dispensed.

- The risk of VTE was lower (non-significantly), with DOAC than LMWH (RR: 0.69, 95%CI [0.42 to 1.16]) with less bleeding (RR: 0.64, [0.43 to 0.97]).
- The mean medical healthcare cost per patient followed during exposure period was €1,492 for patients treated with DOAC and €1,934 for patients treated with LMWH (Table 2).
- The mean cost per patient was lower with DOAC compared to LMWH for drugs (€330 vs. €439), medical visits €204 vs. €208), nursing procedures (€81 vs. 264€), lab tests (€33 vs. €82), hospitalisations €316 vs. €343) and transports (€281 vs. €353) (Figure 2).
- Specific results for apixaban *versus* LMWH were very similar: €1,489 *versus* €1,935 for total medical costs of healthcare resources by patient. The total medical cost was €1,421 for patients treated with other DOAC.

Table 2: General healthcare resources costs and specific costs according to the societal perspective during exposure period in all DOAC vs LMWH groups (matched patients)

	All DOAC				LMWH			
	% ⁽¹⁾	Mean ⁽²⁾	Median ⁽²⁾	[p25% - p75%] ⁽²⁾	% ⁽¹⁾	Mean ⁽²⁾	Median ⁽²⁾	[p25% - p75%] ⁽²⁾
Specific costs in euros								
Total costs		127.3	75.8	[75.8;120.1]		369.9	336.1	[246.1;415.3]
Antithrombotic drugs	100.0	100.2	75.8	[75.8;89.9]	100.0	195.5	184.2	[153.1;215.9]
Specific hospitalisations	0.4	13.0	0.0	[0.0;0.0]	0.6	19.2	0.0	[0.0;0.0]
Medical visits, technical acts	16.3	14.1	0.0	[0.0;0.0]	93.0	155.1	146.8	[79.0;203.6]
Overall costs in euros								
Total costs		1491.8	1160.7	[864.7;1658.0]		1933.5	1528.4	[1179.9;2097.7]
Hospitalisations	9.1	316.2	0.0	[0.0;0.0]	9.5	342.6	0.0	[0.0;0.0]
All drug dispensations	100.0	330.3	265.9	[182.2;385.8]	100.0	439.3	365.2	[272.9;505.1]
Physiotherapy	92.1	415.1	412.2	[268.3;552.9]	93.3	428.7	420.0	[278.0;565.9]
Medical visits, technical acts	97.8	204.4	152.8	[95.5;238.0]	97.6	208.3	153.5	[95.9;239.4]
Nursing acts	84.9	81.3	53.3	[20.1;86.2]	94.3	263.7	253.1	[153.4;322.9]
Transport	22.5	281.1	0.0	[0.0;0.0]	23.9	353.2	0.0	[0.0;0.0]
Products and services	63.1	91.4	29.8	[0.0;97.1]	63.1	103.3	31.8	[0.0;105.3]
Other medical healthcare resources	18.1	55.3	0.0	[0.0;0.0]	18.9	54.9	0.0	[0.0;0.0]
Lab tests	48.9	32.9	0.0	[0.0;44.1]	96.0	82.1	64.8	[42.1;99.9]
Sick leaves and daily allowances	11.4	291.4	0.0	[0.0;0.0]	11.5	298.5	0.0	[0.0;0.0]
Assistances, pensions and disability allowances	8.1	88.5	0.0	[0.0;0.0]	8.5	94.1	0.0	[0.0;0.0]

⁽¹⁾Concerned patients, ⁽²⁾For all patients

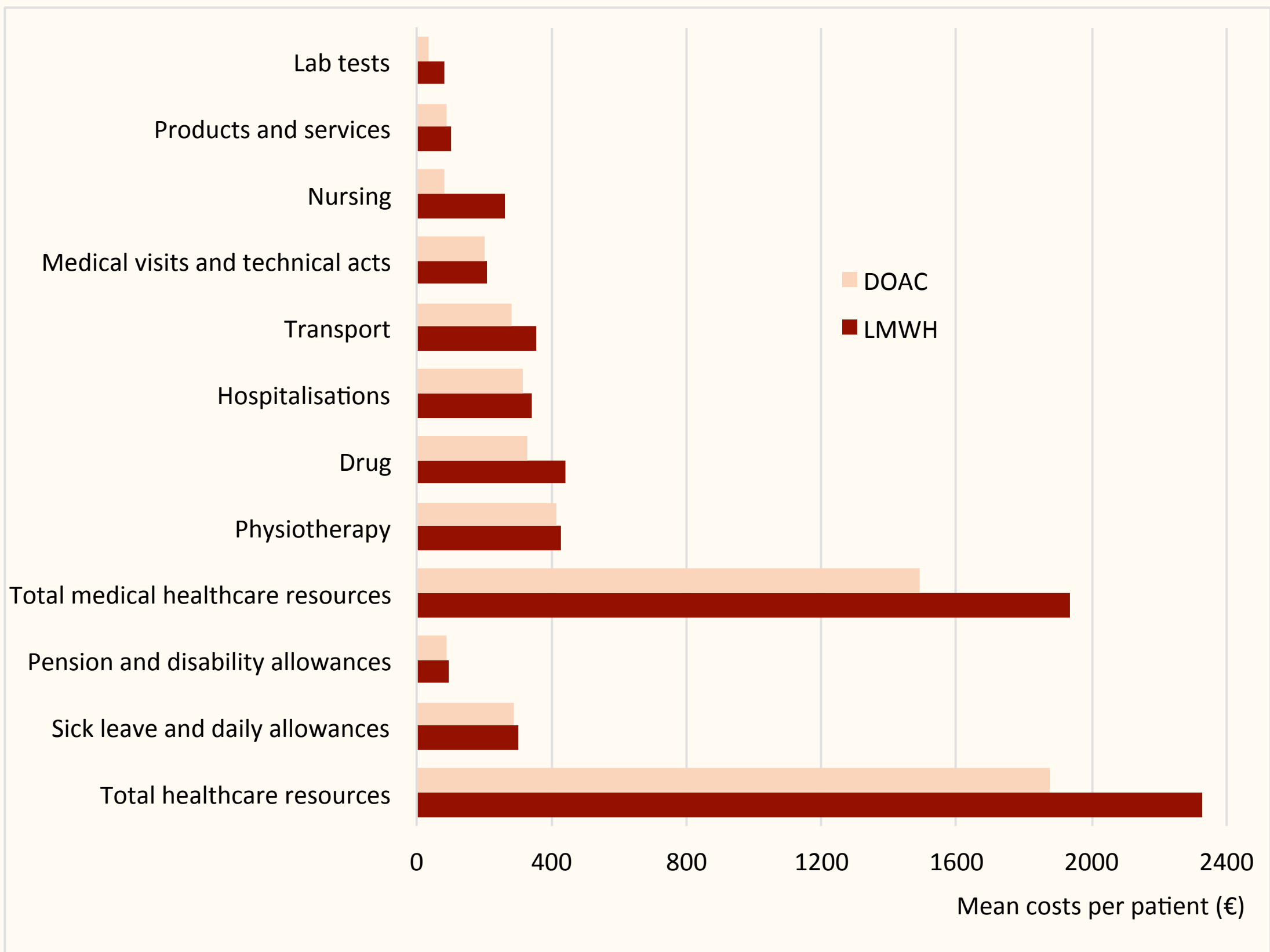


Figure 2: General healthcare resources costs according to the societal perspective during exposure period in all DOAC vs LMWH groups (matched patients)

Conclusion

- The study confirms a better benefit-risk ratio of DOAC compared to LMWH for thromboprophylaxis following TKR in real-life setting, associated with cost savings (25% lower medical costs).
- Patients receiving apixaban at this time provided results similar to all DOAC.