Direct Oral Anticoagulants *vs* Low-Molecular-Weight Heparins for venous thromboembolism prevention following total hip replacement surgery

Comparative effectiveness and medical costs from a French nationwide cohort study of around 120 000 patients

BLIN Patrick, SAMAMA Charles-Marc, SAUTET Alain, MISMETTI Patrick, BENICHOU Jacques, LIGNOT-MALEYRAN Séverine, LAMARQUE Stéphanie, LORRAIN Simon, ***LASSALLE Régis****, GAUDIN Anne-Françoise, COTTE François-Emery, DROZ-PERROTEAU Cécile, MOORE Nicholas*

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Bordeaux PharmacoEpi
Plateforme de recherche en Pharmaco-épidémiologie
CIC Bordeaux CIC1401
INSERM - Université de BORDEAUX - CHU de Bordeaux - Adera
Bâtiment Le Tondu - case 41 - 146 rue Léo Saignat - 33076 Bordeaux Cedex

Conflict of interest statement

- Study supported by an unrestricted grant from Bristol-Myers Squibb and Pfizer
- EMA EUPAS registry No.11521
  - Overseen by independent experts
  - Designed, conducted, and analysed independently by the Bordeaux PharmacoEpi platform

Context

- **Thromboprophylaxis** recommended after orthopaedic surgery to prevent:
  - Deep Vein Thrombosis (DVT), and
  - Pulmonary Embolism (PE)
- **Three direct-acting oral anticoagulants** (DOAC), *apixaban 2.5mg, dabigatran 110mg, and rivaroxaban 10mg*
  - Were granted a European market authorization
  - For the prevention of venous thromboembolic events (VTE)
  - In adult patients, after a total hip or knee replacement (THR or TKR) surgery
- Study requested by the French Health Technology Assessment Agency (HAS)

Objectives

- To assess and compare the **benefit-risk** and **medical costs** of:
  - DOAC versus Low-Molecular-Weight Heparin (LMWH)
  - For venous thromboembolism, major bleeding and death (all-cause) occurrence
  - During 3 months following THR in a real-life setting

Methods

- **Cohort** of patients in the French nationwide claims and hospitalisation database (SNDS, ex-SNIIRAM) with:
  - ≥ 18 years
  - THR hospitalisation (diagnostic related group, DRG code)
  - from Jan. 2013 to Sept. 2014
  - dispensing of DOAC or LMWH within 1 week after THR discharge
  - 3 years of history before THR
  - 3 months of follow-up after THR discharge
- **Groups of treatment:** 1st treatment (DOAC or LMWH) dispensed within 1 week after discharge
- **3-month follow-up period:** from discharge until switch of treatment, death or end of follow-up (91 days)

Outcomes

- **Primary effectiveness outcome:** hospitalization with VTE (main diagnosis)
- **Primary risk outcome:** hospitalization with bleeding (main diagnosis)
- **Sensitive analyses:**
  - **VTE**: hospitalizations (main or associated diagnosis), anticoagulant switch or a high dosage DOAC dispensing, along (± 1 day) with imaging for DVT or PE diagnosis.
  - **Bleeding**: all hospitalizations with bleeding (main or associated diagnosis).
- **Secondary outcome:** all cause death

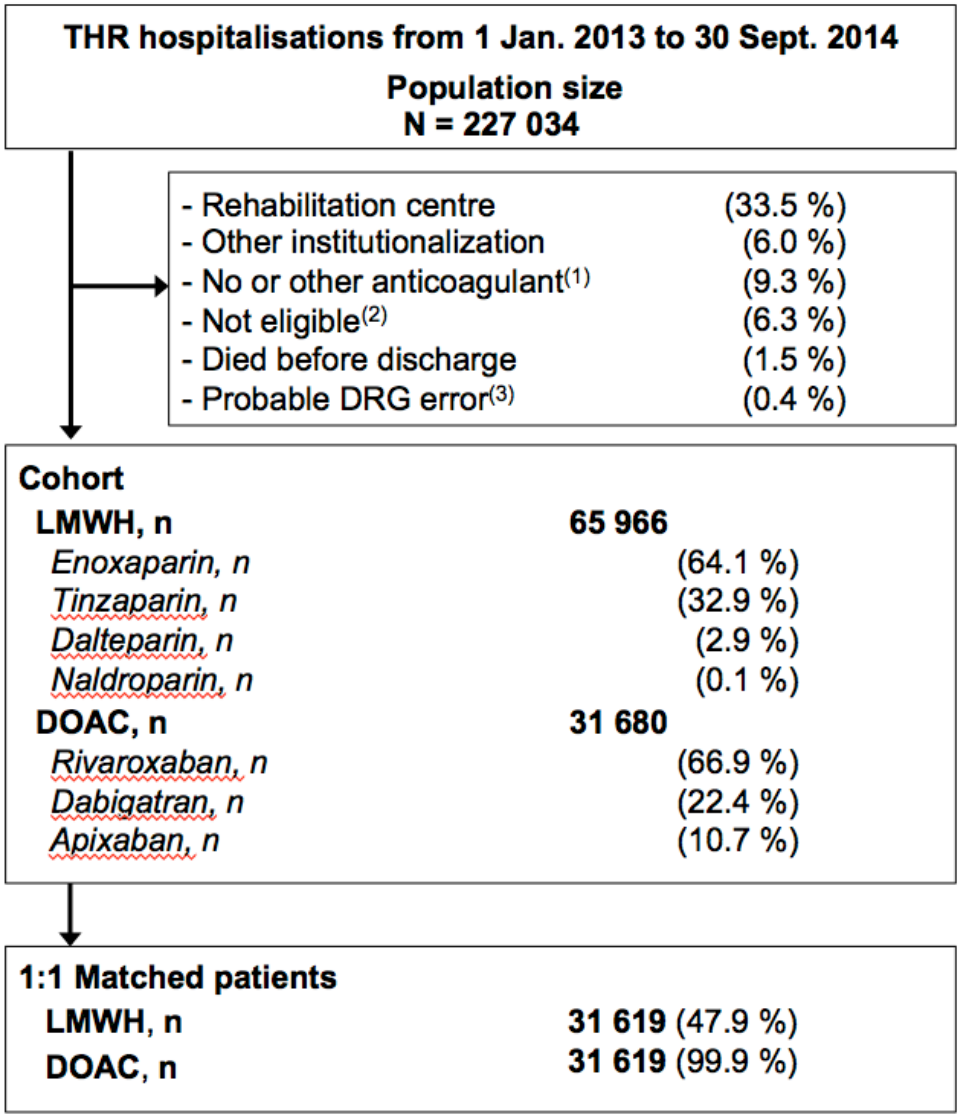
Statistical analysis

- Propensity score (PS): DOAC vs LMWH after THR
- Matching 1:1 of DOAC users with LMWH users on gender, age and logit of PS
- **Comparison of outcomes incidence:** Poisson and quasi-Poisson regression models performed on
  - patients from the global cohort (crude, and with adjustment for logit(PS), age and gender)
  - and on 1:1 matched patients
- **Medical costs** were calculated according to the collective perspective

Propensity score

- **Covariates (X_i)**:
  - Age, gender,
  - THR hospitalization characteristics: duration, hospital category, bleeding diagnosis, hip, pelvis or leg fracture, history of atrial fibrillation,
  - Individual VTE and bleeding risk factors (IMPROVE scores)
  - Other risk factors *(≥1% patients in each group)*: history of cancer, active cancer, rheumatic disease, recent antithrombotic treatment, oral contraception or hormone replacement therapy, antiplatelet agent (acetylsalicylic acid, clopidogrel, prasugrel or ticagrelor) in the week after discharge, acetylsalicylic acid during follow-up

Population selection

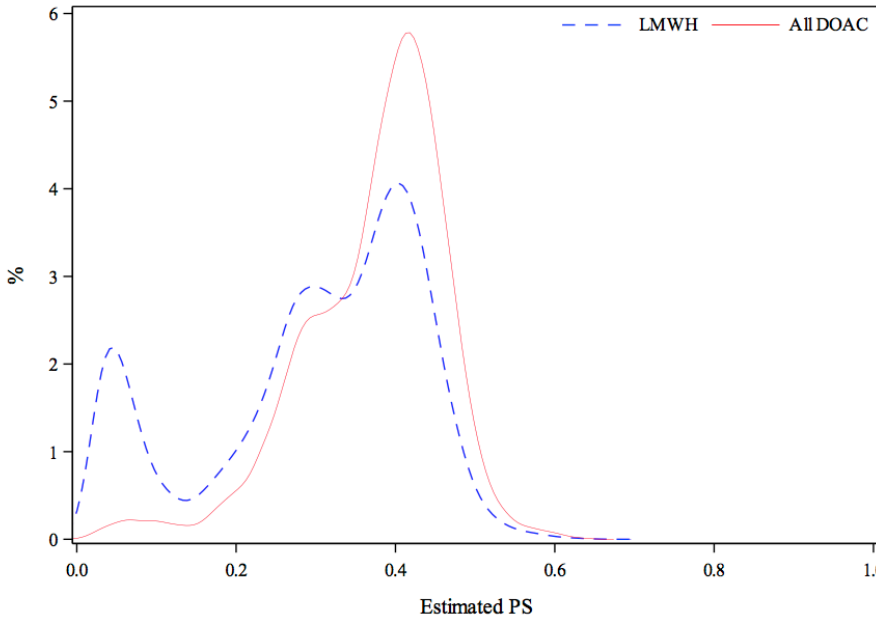


(1) No anticoagulant dispensing found or first dispensing of unfractionated heparin, fondaparinux or vitamin-K antagonist or anticoagulant associations within one week after discharge;

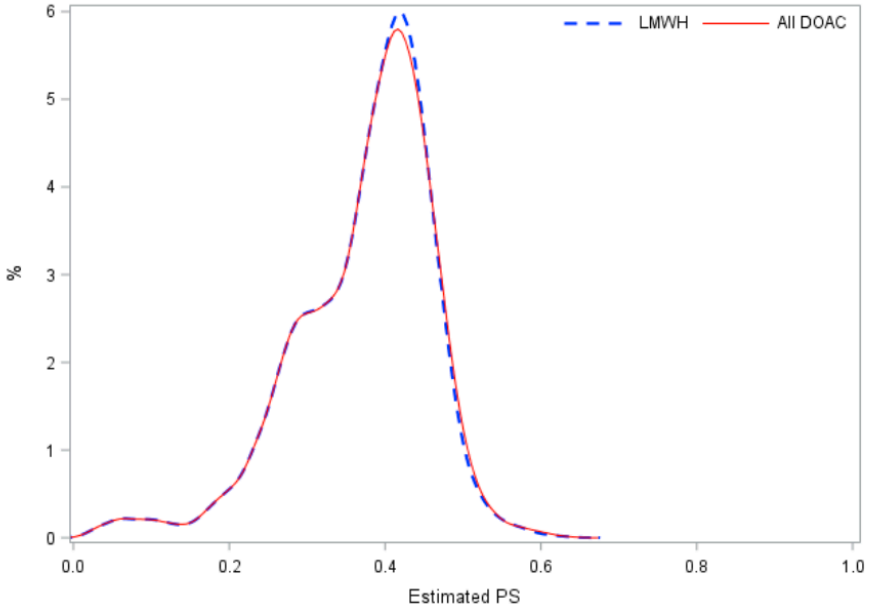
(2) Patient not in the reference directory or, < 18 years or, database history < 3 years or, database follow-up < 3 months or, other than teaching, general or private hospitals;

(3) Discrepancy between Diagnosis Related Group and primary diagnosis for THR.

Propensity score distributions



Overall groups



1:1 matched patients

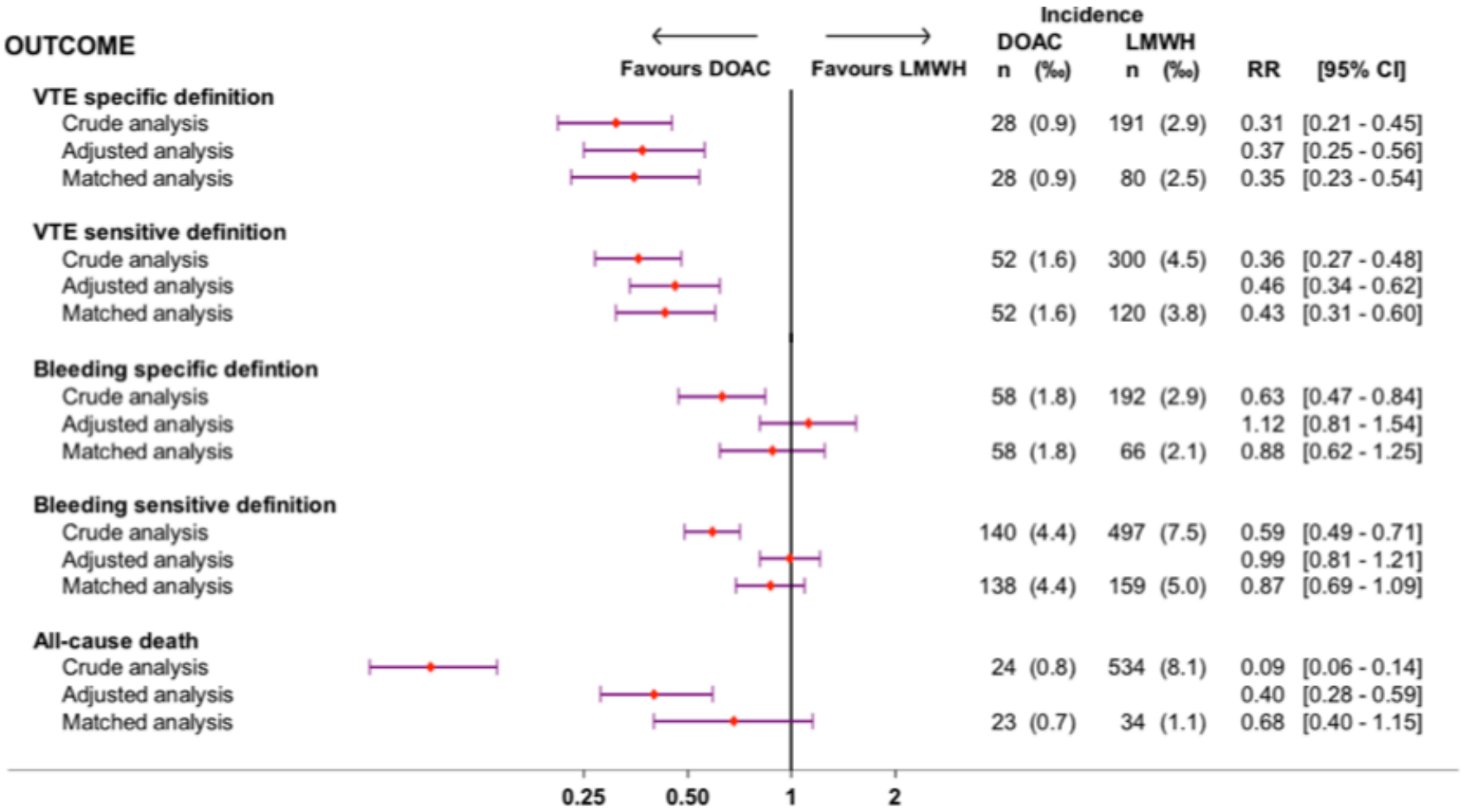
Population description (baseline)

	All patients		Matched patients	Standardized differences, %
	DOAC n = 31 680	LMWH n = 65 966		Crude
Male, %	52.4	47.9		-9.0
Age, mean (SD)	65.7 (10.8)	69.8 (12.0)		35.5
IMPROVE VTE risk score %				16.1
1	27.1	19.3		
2	63.5	69.0		
>3	9.3	11.7		
IMPROVE bleeding risk score, %				11.5
< 2	23.0	21.5		
2 - 3.5	49.0	48.3		
4 - 6.5	27.5	29.1		
≥ 7	0.5	1.2		
Individual VTE or bleeding risk factors				
- Cancer history, %	11.9	14.4		7.4
- Active cancer, %	8.8	10.6		6.4
- Atrial fibrillation, %	3.4	6.6		14.3
- Recent antithrombotic treatment history, %	16.6	28.0		27.8
- Oral contraception or HRT, %	10.9	9.7		-4.1
- Antiplatelet agent in the week after discharge, %	1.9	4.2		13.4
- ASA during follow-up, %	0.9	1.2		2.6
THR index hospitalisation				
- Category of hospital, %				
Teaching hospital	11.4	9.9		-5.0
Other public hospital	12.4	23.6		29.6
Private hospital	76.2	66.5		-21.6
- Duration, mean (SD)	7.0 (2.2)	7.9 (3.5)		30.8
- Hip, pelvis or leg fracture, %	1.9	15.9		50.7
- Bleeding diagnosis during hospitalisation, %	1.3	2.9		11.3
Duration of first antithrombotic treatment dispensing (days), mean (SD)	30.2 (5.9)	27.0 (7.9)		-

Population description (baseline)

	All patients		Matched patients		Standardized differences, %		
	DOAC n = 31 680	LMWH n = 65 966	DOAC n = 31 619	LMWH n = 31 619	Crude	Adjusted	Matched
Male, %	52.4	47.9	52.4	52.4	-9.0	-0.2	0.0
Age, mean (SD)	65.7 (10.8)	69.8 (12.0)	65.8 (10.7)	65.8 (10.7)	35.5	-6.3	0.0
IMPROVE VTE risk score %					16.1	-5.3	-1.0
1	27.1	19.3	27.1	27.1			
2	63.5	69.0	63.6	64.1			
>3	9.3	11.7	9.3	8.9			
IMPROVE bleeding risk score, %					11.5	-4.4	-1.1
< 2	23.0	21.5	23.0	23.1			
2 - 3.5	49.0	48.3	49.0	49.3			
4 - 6.5	27.5	29.1	27.5	27.1			
≥ 7	0.5	1.2	0.5	0.5			
Individual VTE or bleeding risk factors							
- Cancer history, %	11.9	14.4	11.9	11.0	7.4	-2.1	-3.0
- Active cancer, %	8.8	10.6	8.8	8.2	6.4	-1.6	-2.1
- Atrial fibrillation, %	3.4	6.6	3.4	3.1	14.3	-2.2	-2.1
- Recent antithrombotic treatment history, %	16.6	28.0	16.6	16.6	27.8	-3.7	0.0
- Oral contraception or HRT, %	10.9	9.7	10.9	10.5	-4.1	-1.7	-1.1
- Antiplatelet agent in the week after discharge, %	1.9	4.2	1.9	1.8	13.4	0.2	-1.1
- ASA during follow-up, %	0.9	1.2	0.9	0.7	2.6	-0.4	-2.5
THR index hospitalisation							
- Category of hospital, %							
Teaching hospital	11.4	9.9	11.3	10.1	-5.0	8.4	-3.9
Other public hospital	12.4	23.6	12.4	12.8	29.6	-1.8	1.4
Private hospital	76.2	66.5	76.3	77.0	-21.6	-2.6	1.7
- Duration, mean (SD)	7.0 (2.2)	7.9 (3.5)	7.0 (2.1)	7.0 (2.2)	30.8	-5.2	0.9
- Hip, pelvis or leg fracture, %	1.9	15.9	1.9	2.0	50.7	1.5	0.8
- Bleeding diagnosis during hospitalisation, %	1.3	2.9	1.3	1.1	11.3	0.5	-1.7
Duration of first antithrombotic treatment dispensing (days), mean (SD)	30.2 (5.9)	27.0 (7.9)	30.2 (5.9)	27.2 (7.6)	-	-	-

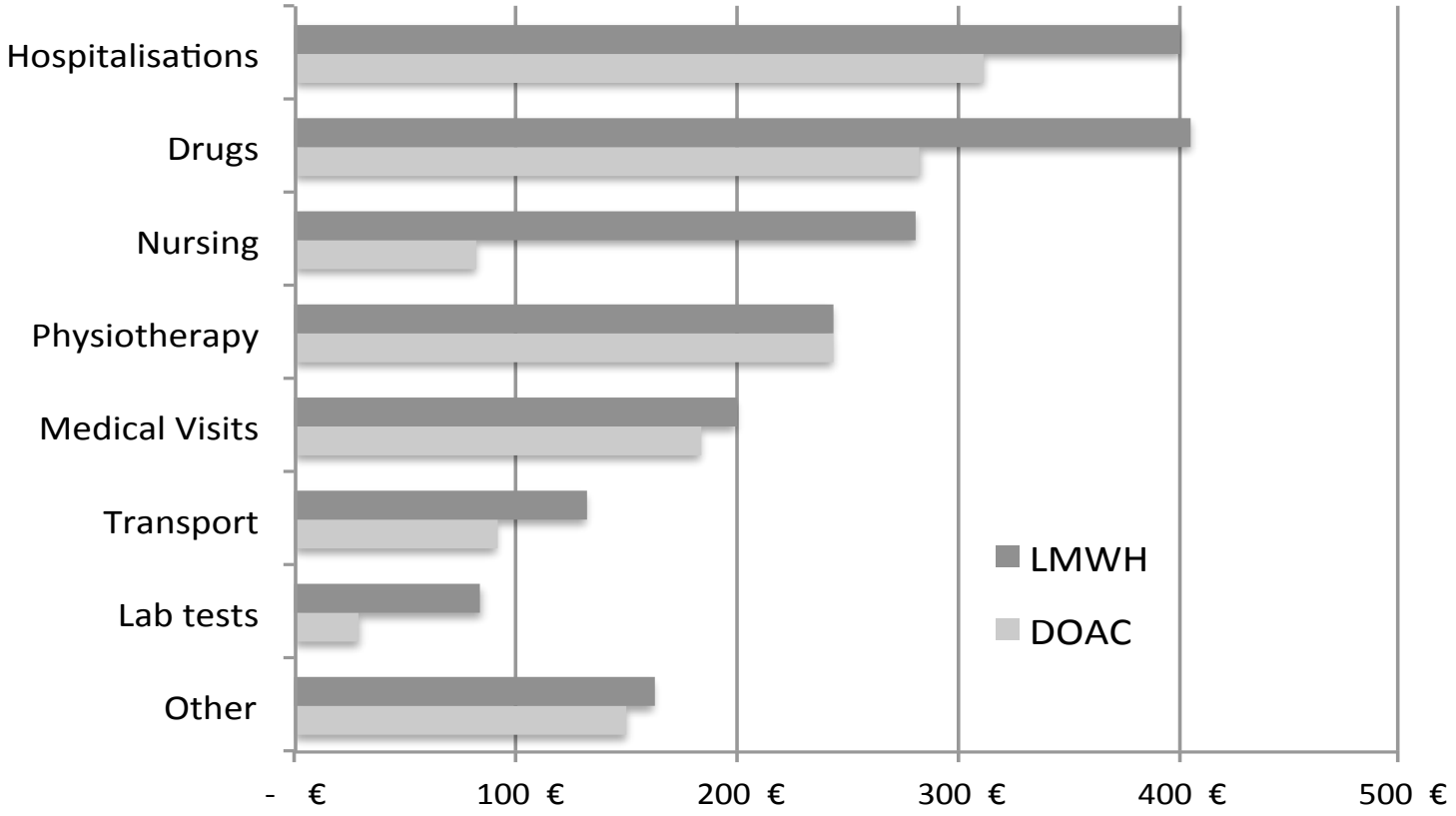
Risk comparison



DOAC = Direct AntiCoagulant; LMWH = Low Molecular Weight Heparin; n = number of events; ‰ = incidence rate per 1000 persons; RR = Relative risk; 95%CI: 95% confidence interval; VTE = Venous Thromboembolic Event.

Medical costs

- Mean medical cost per patient during 3-month follow-up according to the collective perspective (1:1 matched patients)



Discussion

- Claims database
  - little clinical information to validate diagnoses,
  - but good correspondence between DRG and main diagnosis codes
- Results apply only to patients who returned home after discharge
- Residual confounding cannot be excluded:
  - small residual differences (2-5%) but most of the time not in favor of DOAC

Conclusion

- This nationwide cohort study of patients with anticoagulant VTE prevention following THR in real-life setting shows:
  - **a low risk of VTE**, **clinically relevant bleeding and death** after discharge
  - with a **better benefit-risk ratio of DOAC** compared to LMWH, associated with **cost savings**.

THANK YOU FOR YOUR ATTENTION !

*(Results of the total knee replacement study available today on poster **#77**)*

regis.lassalle@u-bordeaux.fr

Bordeaux BPE PharmacoEpi

Bordeaux PharmacoEpi - http://www.pharmacoepi.eu
Plateforme de recherche en Pharmaco-épidémiologie
CIC Bordeaux CIC1401
INSERM - Université de BORDEAUX - CHU de Bordeaux - Adera
Bâtiment Le Tondu - case 41 - 146 rue Léo Saignat - 33076 Bordeaux Cedex
Acc. +33 (0)5 57 57 46 75 – Fax +33 (0)5 57 57 47 40