



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 Blin¹, CM Samama², A Sautet³, P Mismetti⁴, J Benichou⁵, S Lignot-Maleyrans¹, S Lamarque¹, S Lorrain¹, R Lassalle¹, AF Gaudin⁶, FE Cotte⁶, C Droz-Perroteau¹ 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

Abstract



Background: Thromboprophylaxis is recommended after major orthopaedic surgery to prevent the risk of deep vein thrombosis and pulmonary embolism. Three direct-acting oral anticoagulants (DOAC), apixaban, dabigatran, and rivaroxaban, was granted a European market authorization for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective total knee replacement (TKR).

Objectives: To assess the benefit-risk and medical costs of DOAC vs Low-Molecular-Weight Heparin (LMWH) for VTE prophylaxis following TKR in real-life setting. **Methods:** Cohort of all patients with TKR performed in France from Jan-2013 to Sept 2014, home return after discharge, followed-up for 3 months in the French nationwide claims and hospitalization database. Patients treated with a DOAC were 1:1 matched on gender, age, propensity score with those receiving LMWH. Main outcomes were hospitalization with primary diagnosis of VTE or bleeding, and all causes death during the follow-up or anticoagulant switch. Relative risk (RR) between DOAC and LMWH were estimated using quasi Poisson model, with sub-analyses for each DOAC. Medical costs were calculated according to the collective perspective. **Results:** Among the patients who returned home, 15 738 were treated with a DOAC (rivaroxaban 66.2%, dabigatran 22.6%, apixaban 11.2%), 33 497 with LMWH. Mean age was 67.6 (±8.9) years for DOAC patients, 68.5 (±9.5) for LMWH patients, respectively 52.9% and 53% women, a mean duration of hospital stay of 7.7 days and 8.0 days, a mean IMPROVE VTE risk score = 2, a bleeding risk score = 3.5. Almost all DOAC patients (15 720) were matched to a LMWH patient. For them, the risk of VTE was lower with DOAC than LMWH (1.6‰, 2.3‰ respectively, RR= 0.69 [0.42-1.16]) but not significantly, while the risk of bleeding was significantly lower with DOAC (2.4‰ and 3.8‰, RR= 0.64 [0.43-0.97]), without difference for all cause death (0.6‰ and 0.8‰, RR= 0.96 [0.30-1.62]). The mean total medical costs per matched patient was €442 lower with DOAC (-23%), difference been mainly from drugs, nursing and hospitalizations. **Conclusions:** This study shows a low risk of VTE, clinically relevant bleeding and death after discharge for patients with anticoagulant for VTE prevention following TKR with a better benefit-risk ratio of DOAC compared to LMWH, and associated with cost savings.

Background

- Thromboprophylaxis is recommended after major orthopaedic surgery to prevent the risk of Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE).
- Three direct-acting oral anticoagulants (DOAC), apixaban, dabigatran, and rivaroxaban, were granted a European market authorization for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective total hip or knee replacement (THR or TKR) surgery.

Objectives

To assess the **benefit-risk** and **medical costs** of Direct-Oral Anticoagulants (DOAC) vs Low-Molecular-Weight Heparin (LMWH) for venous thromboembolism (VTE) prophylaxis following total knee replacement (TKR) in a real-life setting.

Methods

- Design:** Cohort of all patients with TKR performed in France from Jan-2013 to Sept 2014, discharged to home, followed-up for 3 months in the French nationwide claims and hospitalization database. DOAC users were 1:1 matched on gender, age and propensity score with LMWH users. **Relative risks** (RR) of hospitalized VTE, hospitalized bleeding and death were estimated using quasi-Poisson models. **Medical costs** were calculated according to the collective perspective.

Methods

- Data source:** the **SNDS database** is the nationwide healthcare system database with individual continuous information on all reimbursed outpatient claims, linked to the national hospital-discharge summaries database and the national death registry.
- Endpoints:**
 - The **primary effectiveness outcome** was defined as a hospitalization with VTE main diagnosis.
 - The **primary risk outcome** was defined as a hospitalization with bleeding main diagnosis.
 - For **sensitive analyses**, broader definitions were used:
 - VTE: all hospitalizations with VTE main or associated diagnosis, and non-hospitalized VTE defined as an anticoagulant switch (DOAC, LMWH, Vitamin-K antagonist (VKA), fondaparinux) or a high dosage DOAC dispensing, along (± 1 day) with medical imaging for DVT or PE diagnosis (compression ultrasonography, venography, thoracic CT angiogram, lung scintigraphy).
 - Bleeding: all bleeding hospitalizations with main or associated diagnosis of bleeding.

Declaration of interest 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.

Results

Study population

- Among the 161,724 TKR identified in the SNDS database between 2013 Jan-1st and 2014 Sept-30th, **49,235 were included** (the main reason not to be included was no home return after discharge, mainly for a rehabilitation facility admission):
 - 15,738** were treated with a **DOAC** in the week after discharge (**Figure 1**), mostly rivaroxaban, dabigatran and apixaban (66.2%, 22.6% and 11.2%);
 - 33,497** were treated with **LMWH**, enoxaparin being the most commonly used;
 - ≥ 95 % of DOAC and LMWH** were dispensed **the day of or the day after discharge**, with a median of 30 days of treatment.
- Almost all DOAC patients (≥ 99.8%) included were individually matched to a LMWH patient.

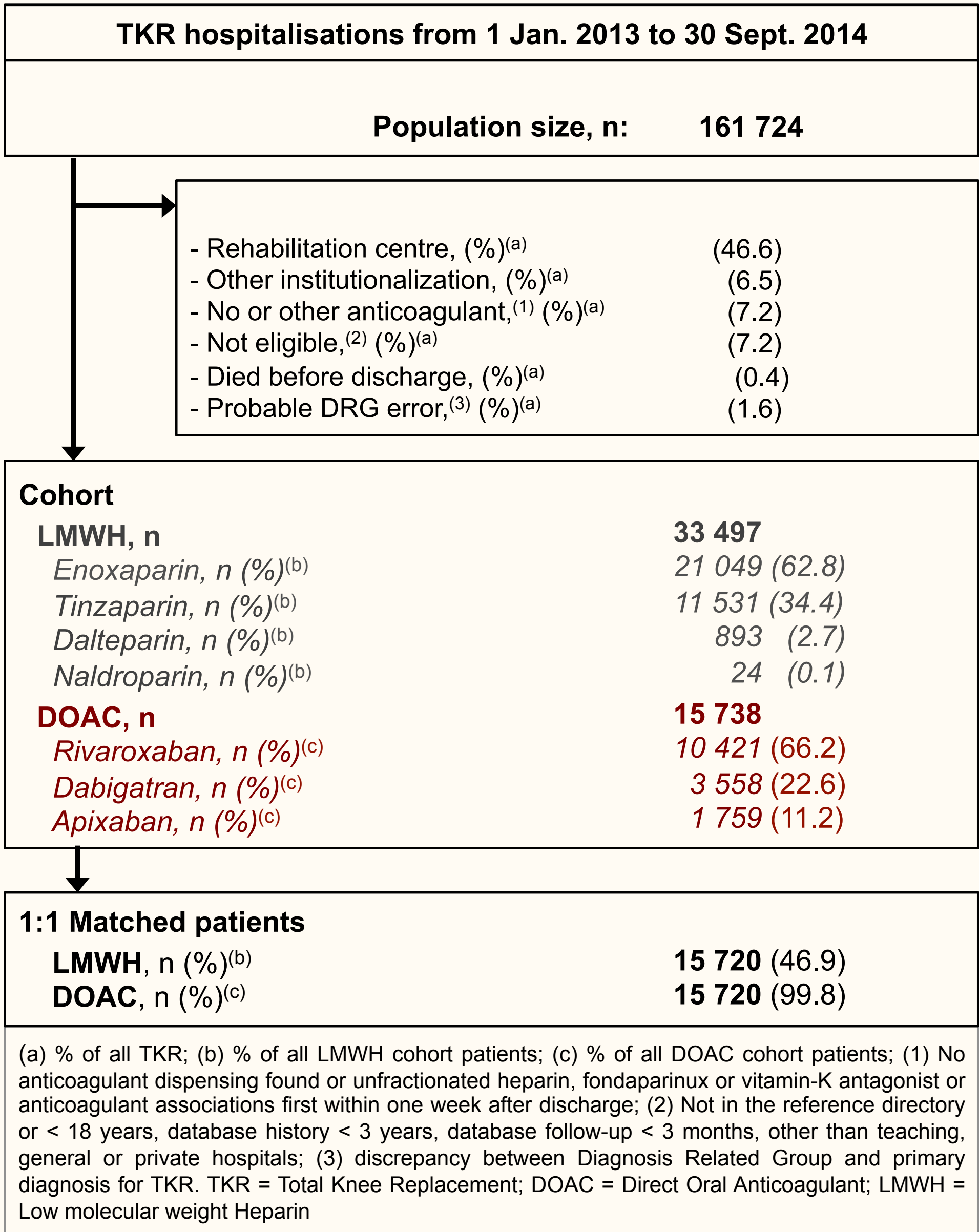


Figure 1: Population flow chart

Population characteristics

Table 1: Characteristics of matched TKR patients according to DOAC and LMWH treatment groups

| | 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 (SD) | 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 |
| - 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 |
| 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 (SD) | 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 hospitalization, % | 1.8 | 2.6 | 1.8 | 1.6 | 5.1 | 0.9 | -1.3 |
| Treatment duration ⁽⁷⁾ (days), mean (SD) | 29.1 (6.9) | 25.6 (8.4) | 29.1 (6.9) | 25.6 (8.3) | - | - | - |

(1) Mean standardized difference; (2) Treatment on-going within the year before TKR; (3) Within 3 month before TKR; (4) Acetylsalicylic acid, clopidogrel, prasugrel or ticagrelor; (5) Estimated from number of units dispensed; TKR = Total Knee Replacement; DOAC = Direct Oral Anticoagulant; LMWH = Low molecular weight Heparin; SD = Standard deviation; HRT = Hormone Replacement Therapy; ASA = Acetylsalicylic acid.

Relative risks

- The **incidence of VTE** (hospitalization main diagnosis) **was lower with DOAC** than LMWH, but **not significantly** (1.6‰ and 2.3‰, RR: 0.69, 95%CI [0.42 to 1.16] (**figure 2**)). With hospitalized and non-hospitalized VTE criteria became significant.
- The **incidence of bleeding** (hospitalization main diagnosis) **was significantly lower with DOAC** than LMWH, 2.4‰ and 3.8‰, RR = 0.64 [0.43 to 0.97].
- The **risk of death** was **non-significantly different** between DOAC and LMWH (0.6‰ and 0.8‰,), RR = 0.69 [0.30 to 1.62].

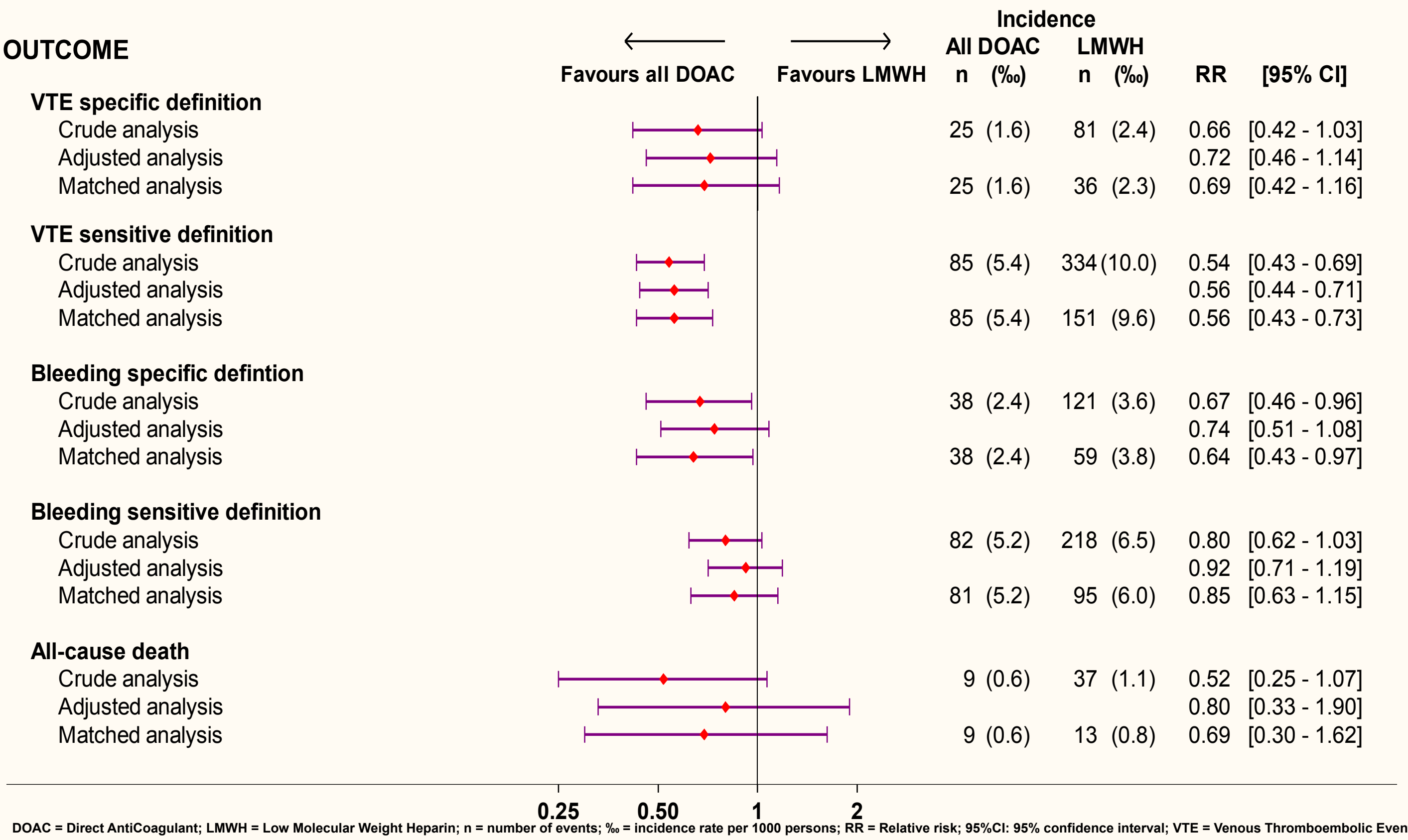


Figure 2: relative risk of VTE, bleeding and death between DOAC and LMWH

Medical costs

- Mean medical cost was **21% lower with DOAC** than LMWH for the 3 months after TKR discharge (€1808 and €2276) (**Figure 3**).
- The difference was mainly from **nursing** (- €183, €81 vs €264), **drugs** (- €109, €330 vs €439), medical transports (- €72, €281 vs €353), lab tests (- €49, €33 vs €82), and hospitalizations (- €27, €316 vs €443): 73% of the total mean difference between DOAC and LMWH came from nursing, drugs and lab tests (39%, 23% and 11%), 6% from hospitalizations and 15% from medical transports.
- DAOC and LMWH mean costs were similar for medical visits, physiotherapy, and other costs.

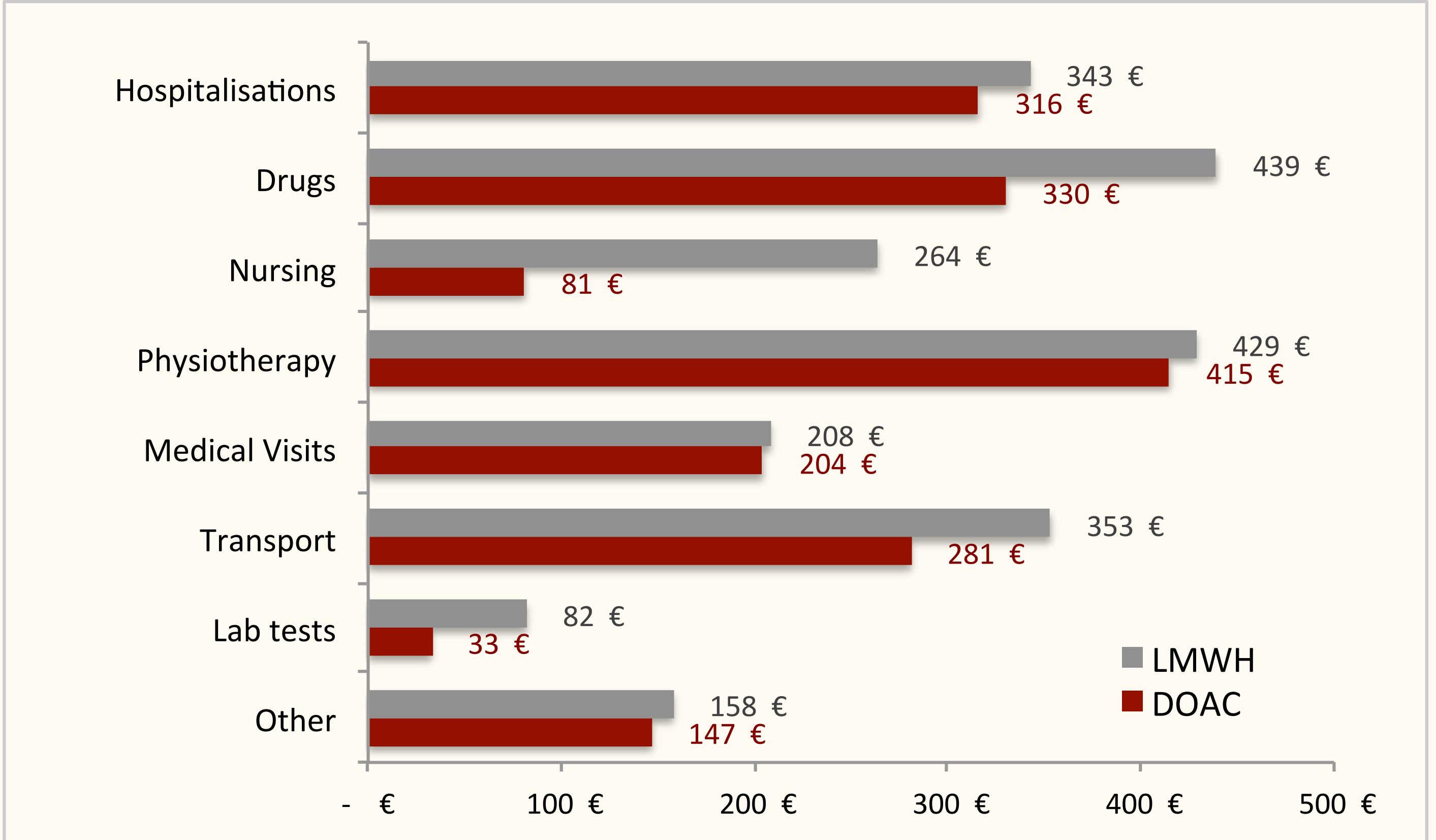


Figure 3: Medical costs according to the collective perspective for DOAC and LMWH matched patients

Conclusions

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