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Comparative effectiveness of direct oral anticoagulants versus low-molecular weight heparins for the prevention of venous thromboembolism after total hip or knee replacement: A nationwide database cohort study

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1 Comparative effectiveness of direct oral anticoagulants versus low-molecular weight heparins
2 for the prevention of venous thromboembolism after total hip or knee replacement: a
3 nationwide database cohort study

4
5 Running title: DOAC versus LMWH after total hip or knee replacement

6
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22

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25

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31

32

33 Abbreviations:

34 CI: confidence interval

35 DOAC: Direct-acting oral anticoagulants

36 DVT: deep vein thrombosis

37 HR: hazard ratio

38 ISTH: International Society on Thrombosis and Haemostasis

39 LMWH: low-molecular weight heparin

40 PE: Pulmonary embolism

41 RR: Relative Risk

42 SNDS: Système National des Données de Santé

43 THR: total hip replacement.

44 TKR: total knee replacement

45 VTE: venous thromboembolism

46

47

48 **Abstract**

49 Background:

50 Venous thromboembolism (VTE) after total knee or hip replacement (TKR, THR) is
51 usually prevented with low-molecular weight heparin (LMWH), and increasingly by
52 direct oral anticoagulants (DOAC). The aim of the present study was to compare the
53 benefit-risk and medical costs of DOAC vs. LMWH in a real-life setting.

54

55 Methods

56 All patients with THR or TKR in France between Jan-1st 2013 and Sep-30th 2014,
57 discharged to home, were identified and followed-up for 3 months in the French
58 nationwide claims database, SNDS. DOAC users were 1:1 matched with LMWH users on
59 gender, age and propensity score. Relative risks (RR) of hospitalized VTE, hospitalized
60 bleeding and death were estimated using quasi-Poisson models. Medical costs were
61 calculated according to the societal perspective, including total cost for outpatient
62 claims and national DRG costs for hospitalisations.

63

64 Results:

65 Most DOAC users ($\geq 98.8\%$) were matched to a LMWH patient. For the 63,238 matched
66 THR patients, the 3-month absolute risk of VTE was 0.9‰ with DOAC and 2.5‰ with
67 LMWH (RR = 0.35 [0.23 to 0.54]), of bleeding 1.8‰ and 2.1‰ (0.88 [0.62 to 1.25]),
68 death 0.7‰ and 1.1‰ (0.68 [0.40 to 1.15]). For the 31,440 matched TKR patients, risks
69 were 1.6‰ and 2.3‰ (0.69 [0.42 to 1.16]) for VTE, 2.4‰ and 3.8‰ (0.64 [0.43 to 0.97])
70 for bleeding, and 0.6‰ and 0.8‰ (0.69 [0.30 to 1.62]) for all-cause death. Mean medical
71 costs were 28% and 21% lower with DOAC than LMWH for THR and TKR, respectively.

72

73 This nationwide study found a very low risk of VTE, hospitalized bleeding and death after
74 THR or TKR discharge in patients with VTE prevention in real-life setting, with better
75 benefit-risk profiles of DOAC compared to LMWH, and associated cost savings.

76

77

78 **1. Introduction**

79 Thromboprophylaxis is recommended after major orthopedic surgery to prevent the risk of
80 deep vein thrombosis (DVT) and pulmonary embolism (PE) (1-3). Three direct oral
81 anticoagulants (DOAC), apixaban 2.5 mg (bid), dabigatran 110 mg (bid), and rivaroxaban 10
82 mg (od), were granted an European market authorization for the prevention of venous
83 thromboembolic events (VTE) in adults after elective total hip or knee replacement (THR,
84 TKR). In randomized controlled trials, they showed non-inferiority or superiority to 40 mg of
85 enoxaparin, a low-molecular weight heparin (LMWH) (4-9), without increasing major
86 bleeding.

87 However, these clinical trials included a limited number of patients with too few symptomatic
88 VTE to reach statistical power for comparisons. To overcome this limit, the primary efficacy
89 outcome was defined as the composite of asymptomatic and symptomatic DVT, non-fatal PE
90 and death from any cause, the clinical relevance of which is disputable in the face of a high
91 ratio of asymptomatic DVT to symptomatic VTE (10) and high rate of false positives from
92 imaging performed for another reason.(11) A meta-analysis of 16 trials of DOAC versus
93 enoxaparin to assess symptomatic VTE after THR or TKR still had few events and wide 95%
94 confidence intervals (95%CI) for each drug comparison (12).

95 Furthermore, the impact of anticoagulant thromboprophylaxis in real-life is probably not the
96 same when physician practice, patient characteristics, drug use and prescription, and care
97 management are not standardized as they are in clinical trials (13, 14). Several real-world
98 cohort studies using claims databases were published for other indications of DOAC, such as
99 stroke prevention in atrial fibrillation (15-19) or treatment of VTE (20), but only one was
100 found for thromboprophylaxis after major orthopedic surgeries (21). The present study was
101 designed to compare the risk of VTE, bleeding and death in clinical practice between all

102 DOAC and LMWH, as well as for each DOAC, during the 3-month post-discharge period
103 after THR or TKR, using the French nationwide healthcare systems database, SNDS.

104

105

106 **2. Materials and methods**

107 **2.1. Research question and objectives**

108 To compare the 3-months event rates of VTE, bleeding or death in patients treated with a
109 DOAC or LMWH after total knee or hips replacements;

110

111 **2.2. Design:**

112 This was a high-dimensional propensity-score (hdPS) matched cohort study of all out-patients
113 dispensed DOAC or LMWH during 3 months, after THR or TKR, in France from January 1,
114 2013 to September 30, 2014.

115

116 **2.3. Study Setting**

117 SNDS is the national healthcare data system in France. It links the nationwide
118 mandatory public health insurance system claims database SNIIRAM, to the national
119 hospital discharge database PMSI and to the national death registry CépiDC. It includes
120 more than 99% of the French population (66 Million persons in 2013) from birth (or
121 immigration) to death (or emigration), even if a subject changes occupation or retires,
122 and irrespective of socioeconomic status. The SNDS contains individual pseudonymized
123 information on all medical and paramedical encounters, drugs claims, hospital
124 admissions and procedures, and date of death, that are linked to create a longitudinal
125 record of outpatient health encounters, hospital diagnoses and drug dispensing.(22)
126 SNDS includes the hospital discharge summaries database, which includes all hospital
127 discharge summaries from all private or public hospitals with main, associated and
128 secondary diagnoses. Procedures are also recorded, as are the more expensive drugs or
129 implantable devices.

130 Diagnoses may be identified from:

131 - Registration for long-term diseases (LTD, over 4000 ICD-10 codes) that warrant full
132 healthcare coverage with no co-payment. This registration is requested by the patient's
133 physicians (outpatient or hospital), and diagnoses are verified by the healthcare
134 insurance system. Registration is not mandatory. It may be missing for instance if the
135 medical expenses are already covered by another chronic disease or the treatment is not
136 expensive. LTD concern background diseases and are not directly related to any
137 individual medical encounter. They are therefore not used for outcomes, only for
138 baseline patient description parameters.

139 - Hospital discharge diagnoses (main, associated, secondary), which will inform on the
140 reason for admission (main), and on background risk modifiers (e.g., diabetes, renal
141 failure, coronary heart disease) that modify the hospital costs. Associate diagnoses
142 inform on reasons for procedures as main diagnosis. They also include disease related
143 group (DRG) cost coding system, and most expensive drugs out of DRG cost. Diagnostic
144 codes are input by the hospital physician in charge of the patient, assisted by professional
145 coders. The quality of the coding is the object of regular internal and external audits, from
146 within the Hospital information systems and fro the national healthcare system within the
147 national accreditation process. When verified, the positive predictive values of the codes in
148 the cardiovascular field were 85% or higher, improving over time. (23-27)

149 - Drug, laboratory, imaging or other procedures, as outpatient or inpatient, whose
150 combinations may be diagnostic. (28)

151 THR studies using SNDS have been published (29, 30), as well as several studies with our
152 major outcomes of interest (19, 31-34).

153

154 **2.4. Study Subjects**

155 All adult (age \geq 18) patients who underwent THR or TKR in France between 1st January 2013
156 and 30th September 2014 were identified in SNDS, (22) using diagnostic related groups
157 (DRG) from hospitalization discharge summaries. Patients who were discharged to home with
158 a dispensing of a DOAC (apixaban, dabigatran, rivaroxaban) or LMWH within a week after
159 discharge, a 3-year look-back period before THR or TKR and a follow-up of three months
160 were included in the cohorts. Patients admitted to a rehabilitation facility were not included
161 because their drug prescriptions are not available in the database.

162 Chronic medical conditions, cardiovascular risk factors, previous and concomitant drug
163 dispensings, and hospital admission diagnoses were collected over the three years
164 previous to the index date. These baseline covariates were included in the propensity
165 score.

166

167 **2.5. Follow-up**

168 Follow-up began at discharge, (index date) and continued until patient death, treatment
169 switch to another anticoagulant, occurrence of an outcome of interest (for that outcome
170 only), or the end of the study period (three months), whichever came first. There was no
171 loss to follow-up.

172

173 **2.6. Outcomes:**

174 The primary effectiveness outcome was defined as a hospitalization with a main diagnosis of
175 VTE (I801-9, I81, I82 ICD-10 codes for VTE, and I26 for PE). The primary safety outcome
176 was hospitalization with a main diagnosis of bleeding (ICD-10 codes detailed in
177 supplementary materials). For sensitivity analyses, broader definitions were used for both
178 outcomes. For VTE, it took into account all hospitalizations with VTE as main or associated
179 diagnosis, and non-hospitalized VTE defined as an anticoagulant switch (to DOAC, LMWH,

180 Vitamin-K antagonist (VKA), fondaparinux) or dispensing of a higher dosage of DOAC,
181 along (\pm 1 day) with medical imaging for DVT or PE (compression ultrasonography,
182 venography, thoracic CT angiogram, lung scintigraphy). For bleeding, sensitivity analysis
183 included all hospitalizations with main or associated diagnosis of bleeding.

184

185 **2.7. Statistical analysis**

186 The conditional probability to be treated by DOAC or LMWH was estimated using propensity
187 scores for each type of surgery (THR and TKR) according to the following patient and
188 disease characteristics at inclusion: age, gender, hospitalization duration, hospital category
189 (university, public, private), bleeding diagnosis during hospitalization, hip, pelvis or leg
190 fracture at index hospitalization, history of atrial fibrillation, other risk factors concerning at
191 least 1% of patients in each group: history of cancer, active cancer (treatment ongoing within
192 the year before THR or TKR), rheumatic disease, recent antithrombotic treatment (\leq 3 month
193 before THR or TKR), oral contraception or hormone replacement therapy, antiplatelet agents
194 (acetylsalicylic acid, clopidogrel, prasugrel or ticagrelor) in the week after discharge,
195 acetylsalicylic acid during follow-up, as well as individual VTE and bleeding risk factors
196 identified by the IMPROVE research group for hospitalized medical patients (35, 36); VTE
197 and bleeding IMPROVE risk score are presented in table 1 for descriptive purpose.

198 Propensity score distributions were examined to check the overlap between two groups before
199 and after matching (see supplementary materials).

200

201 DOAC patients were 1:1 matched to LMWH patients separately for THR and TKR, on
202 gender, age and propensity scores using the Greedy method (without replacement) with a
203 caliper of 0.2 of the standard deviation of the logit of the propensity scores (37). For each
204 DOAC, apixaban, dabigatran and rivaroxaban, versus LMWH, patients were individually

205 matched to LMWH patients with the same method and a ratio of 1:6, 1:3 and 1:1,
206 respectively, to have approximately the same number of LMWH patients in each of the three
207 comparisons.

208 Medical costs were calculated using total cost of the claims and mean cost from the national
209 private and public hospital annual study of cost according to hospital stay group and
210 diagnostic related group (collective perspective).

211

212 Initial characteristics are presented for the matched DOAC and LMWH patients with
213 standardized differences (expressed as a percentage). A standardized mean difference of 10%
214 or less indicates a negligible difference between groups (38). Absolute risk of each outcome
215 was also calculated for all patients (supplementary material) and matched patients. The
216 relative risk (RR) of each outcome and its 95% confidence interval (95%CI) was estimated
217 using quasi-Poisson models for DOAC compared to LMWH. Statistical analysis was
218 conducted using SAS[®] software (Version 9.4, SAS Institute, North Carolina, USA).

219

220 **2.8. Ethics**

221 The protocol was reviewed and approved by the French health authorities (HAS), and
222 received all legal authorizations from the National data-protection commission (CNIL). The
223 study was registered with the EUPAS registry as 11521, conducted according to ENCePP
224 guidance endorsed by the European Medicines Agency on best practices for conducting and
225 reporting Post-authorization safety studies (PASS) using electronic healthcare data sets, and
226 follow the STROBE guidelines.

227

228 **3. Results**

229 During the 21-month inclusion period, 227,034 THR and 161,724 TKR were identified in the
230 SNDS database, and 97,646 and 49,235, respectively, were included in the THR and TKR
231 cohorts (figure 1). The main reason for non-inclusion was transfer to a rehabilitation facility.
232 Other reasons included no anticoagulation or presence of other anticoagulants (unfractionated
233 heparin, fondaparinux, vitamin K antagonists, or two or more anticoagulants) dispensed
234 within a week after initial hospital discharge. A few patients died during index hospitalization
235 or had probable DRG or main diagnosis miscoding (figure 1). For both surgical procedures,
236 around one third of the patients received a DOAC, mostly rivaroxaban, followed by
237 dabigatran and apixaban (66.7%, 22.5% and 10.8%, respectively), and two thirds were treated
238 with LMWH, enoxaparin being the most commonly used, followed by tinzaparin, dalteparin
239 and nadroparin (63.7%, 33.4%, 2.8% and 0.1%, respectively) (figure 1). For most patients (>
240 95%), DOAC and LMWH were dispensed on the day of discharge or the day after, with an
241 average of 30 days of Table 1). Almost all DOAC patients ($\geq 99.8\%$) were individually
242 matched to a LMWH patient, 31 619 for THR and 15 720 for TKR (figure 1).

243

244 The mean age of THR and TKR patients was 68.5 and 68.2 years, 50.6% and 53.0% were
245 women, with a mean duration of hospital stay of 7.6 and 7.9 days, respectively. The median
246 IMPROVE VTE risk score was 2 and bleeding risk score was 3.5 for both surgical
247 procedures. For THR, patients in the DOAC group were younger than LMWH patients, more
248 often male, with a slightly lower VTE and bleeding risk scores, mainly because of age
249 difference, with one day more for the mean hospital stay duration, more often from private
250 hospitals, while the differences between DOAC and LMWH were less marked for TKR
251 patients (supplementary material). All these characteristics were very similar for the three
252 DOAC (apixaban, dabigatran and rivaroxaban), except for more use of apixaban from public

253 hospitalizations (supplementary material). After matching, DOAC and LMWH patients were
254 well balanced for both THR and TKR populations with standardized differences below 5%
255 for all variables (table 1) and good overlap of propensity scores distributions (supplementary
256 material).

257

258 The absolute risk of VTE (hospitalization main diagnosis) for matched patients during the 3-
259 month follow-up after THR hospitalization discharge was significantly lower with DOAC
260 than LMWH for THR (0.9‰ and 2.5‰, respectively), but not significantly for TKR (1.6‰
261 and 2.3‰, respectively) (table 2). Using hospitalized and non-hospitalized VTE criteria,
262 results remained significant for THR and became significant for TKR (table 2). Absolute risk
263 of individual events showed that PE represented about two thirds of VTE hospitalizations,
264 and less than one third when hospitalized and non-hospitalized VTE were considered
265 (supplementary material).

266

267 The absolute risk of hospitalized bleeding (hospitalization main diagnosis) during the 3-
268 month follow-up after TKR hospitalization discharge was also lower with DOAC than
269 LMWH, not significantly for THR (1.8‰ and 2.1‰, respectively, HR 0.88 [0.62 to 1.25])
270 and significantly for TKR (2.4‰ and 3.8‰, respectively, HR 0.56 [0.43 to 0.73]) (table 2).

271 Major bleeding, using the ISTH definition (39), represented more than half of bleeding
272 hospitalizations for both treatment groups and both surgery procedures (supplementary
273 material).

274

275 The risk of death was not significantly different between DOAC and LMWH for THR or
276 TKR (table 2). For each individual DOAC, relative risks point estimates for VTE,

277 hospitalized bleeding and death were similar to all DOAC pooled, but with wider 95%CI in
278 relation with lower number of event and patients exposed, especially for apixaban (Table 2).
279
280 Mean medical cost was 28% lower with DOAC than LMWH for the 3 months after THR
281 discharge (€1374 versus €1906), and 21% lower for TKR (€1808 and €2276), respectively.
282 The mean difference for THR was mainly from nursing (- €199, €82 versus €281), drugs (-
283 €122, €283 versus €405), hospitalizations (- €89, €312 versus €401), lab tests (- €55, €29
284 versus €84), and transports to visit for medical or paramedical care (-€40, €91 versus €132);
285 70% of the total mean difference between DOAC and LMWH came from nursing, drugs and
286 lab tests (37%, 23% and 10%, respectively), 17% from hospitalizations and 8% from medical
287 transports (Figure 2). For TKR, the difference was mainly from nursing (- €183 €, €81 versus
288 €264), drugs (- €109, €330 versus €439), medical transports (- €72, €281 versus €353), lab
289 tests (- €49, €33 versus €82), and hospitalizations (- €27, €316 versus €443): 73% of the total
290 mean difference between DOAC and LMWH came from nursing, drugs and lab tests (39%,
291 23% and 11%, respectively), 6% from hospitalizations and 15% from medical transports
292 (Figure 2). On the other side, DOAC and LMWH average costs were similar for medical
293 visits, physiotherapy, and other costs for both THR and TKR.

294

295

296

297 **Discussion**

298 This nationwide cohort study of about 100 000 THR and 50 000 TKR who returned home
299 after discharge is the first large study comparing DOAC and LMWH for post-surgical
300 thromboprophylaxis in a real-life setting. In patients sharing the same characteristics, it shows
301 that the risk of hospitalized VTE within 3 months after hospital discharge for THR was 65%
302 lower with DOAC than LMWH, without any increase of hospitalized bleeding risk or death,
303 associated with a 28% medical cost saving. For TKR, the lower risk of VTE with DOAC was
304 not significant, but associated with a 36% lower risk of hospitalized bleeding, no death
305 increase, and 21% medical cost saving. Moreover, since the study included all patients in the
306 country, one might consider the point estimates as sufficient to conclude that the risk of VTE,
307 hospitalized bleeding and death for 3 months after discharge was lower with DOAC than with
308 LMWH for THR (by 65%, 12% and 32%, respectively), and TKR (by 31%, 36% and 31%,
309 respectively). These results are consistent with a recent network meta-analysis that concluded
310 to a superiority of DOAC over LMWH. (40)

311

312 SNDS is the nationwide healthcare claims and hospitalization database that covers 99% of the
313 French population. It is fully representative of the French population. It provided the
314 opportunity to identify all THR and TKR performed in France during the inclusion period
315 with exhaustive information about public and private hospitalizations with high specificity of
316 diagnosis for THR, TKR and outcomes, as well as reimbursed outpatient healthcare resources
317 including reimbursed drugs. The main limit is that the database was built for administrative
318 and reimbursement purposes with little clinical information that could be useful to validate
319 diagnoses, to assess disease severity and some behavioural risk factors. However, for THR
320 and TKR, the procedure is well identified through DRG, and furthermore the information was

321 checked with discharge diagnoses leading to exclude very few patients with probable DRG or
322 main diagnosis miscoding (figure 1).

323

324 Another difficulty of such administrative databases is the diagnostic validity of outcomes. In
325 this study, the main analysis used main hospitalization diagnoses to have a very specific
326 definition that minimized the risk of false positives, but concerned more severe cases, i.e. PE
327 and major bleeding. Broader definitions take into account less severe cases (associated
328 diagnosis from hospitalization, non hospitalized VTE) to minimize the risk of false negatives,
329 which provides relative risks that strengthen the robustness of study results. Coding in the
330 hospital database is done by the physician in charge of the patient, assisted by professional
331 medical information technicians. These codes are subject to quality assurance processes to
332 obtain accreditation and certification, and to regular audits from the insurance payer system to
333 ensure the quality of the coding. (41) Major cardiovascular outcomes have been validated,
334 with positive predictive values around 90%, improving over time. (23-27)

335

336 Residual confounding cannot be excluded for comparisons in observational studies. In this
337 study, the matched groups were very well balanced with the 1:1 propensity score matching for
338 main characteristics and known VTE and bleeding risk factors. Furthermore, the few small
339 residual differences between DOAC and LMWH were most of the time not in favor of
340 DOAC, limiting the risk of residual confounding that could explain the lower risk found with
341 DOAC compared to LMWH.

342

343 Another limit is that results apply only to patients who returned home after discharge. Those
344 who did not represented a large part of the THR and TKR populations (figure 1), and were
345 excluded because their drug information including anticoagulant use was not available in the

346 database. Most of them went to a rehabilitation facility. Although their characteristics, VTE
347 and bleeding risk factors were not the same, the risk of VTE during the follow-up was quite
348 the same (supplementary materials), while rates of hospitalized bleeding and death were
349 higher due to older age. This population will have to be specifically studied.

350

351 Our results do not apply also to events occurring during index hospitalization for which a
352 global estimation of VTE, bleeding and death risks has been done, but could not be attributed
353 to DOAC or LMWH, because their use was not registered in the database. For those without
354 event, it is highly probable that the same drug was prescribed before and after discharge, but
355 for those with a VTE event, the drug and dosage initially prescribed in hospital would most
356 probably be changed after the occurrence of an event. The presence of in-hospital bleeding
357 was however included in the determination of the propensity score. Patients with a VTE event
358 during hospitalization should be treated by VKA, high-dose DOAC or fondaparinux and were
359 consequently not included in this analysis.

360

361 Apixaban and rivaroxaban trials for registration demonstrated a better efficacy compared with
362 40 mg enoxaparin, and non-inferiority for dabigatran, without increasing the haemorrhagic
363 and death risks (4-9). Randomized controlled trials are the gold standard to assess treatment
364 efficacy, but may have limited external validity (13, 14). Furthermore, these trials had also
365 several limitations with a composite criterion including symptomatic and non-symptomatic
366 VTE and deaths, and only between 64 % and 76 % of the randomized patients in the modified
367 intent to treat analysis. For symptomatic VTE, as for major bleedings and deaths, the number
368 of events was very low in 6 studies, with insufficient statistical power for the comparison of
369 anticoagulants, except for symptomatic VTE with rivaroxaban versus enoxaparin in TKR (7).

370

371 Although our study was not randomized, its real-life results go in the same direction as those
372 from clinical trials (4-9), as well as the meta-analysis of orthopedic surgery trials (12), but
373 with a better bleeding risk profile. Death was not analyzed in those trials. A recent meta-
374 analysis of all DOAC versus enoxaparin trials did not reach the same conclusions, but it
375 mixed orthopedic and medical patients, different dosages and treatment durations (42).
376 However, despite the inclusion of almost 100,000 matched THR and TKR over 21 months in
377 one of the largest European countries, there were very few actual outcome events. This
378 resulted in limited study power, precluding meaningful direct comparisons of symptomatic
379 events or death with individual anticoagulants.

380 Another result of this study is a very low risk of VTE after discharge in real life, between 3
381 and 10 per 1 000 patients using main hospitalization discharge diagnoses, according to
382 surgical procedures and treatment groups, far from historical background risks (2), and also
383 lower than but close to the last estimation of the American College of Chest Physicians for
384 LMWH (1). The prevention with anticoagulant reduces VTE risk, but a large part of this low
385 risk is due to the development of enhanced rehabilitation after surgery (ERAS) including
386 minimally invasive surgery, improvement of post-surgical care with early mobilization, as
387 well as shorter and shorter hospitalization durations (43). It might be worthwhile to better
388 characterize in the future patients and situations with weak VTE risk for whom the risk of
389 severe bleeding could overcome the benefit of anticoagulants (44), and for whom aspirin
390 might be more suitable. (45)

391

392

393 The cost analysis applied to the French healthcare system and is not directly generalizable.
394 However, at least 70% of the difference between two groups was related to the price of the

395 drug, to nurse care linked with LMWH injections (daily or twice daily), and to lab tests for
396 surveillance. These could be easily extrapolated to other settings.

397 The event rates may also be applied to other contexts, taking into account the relevant cost
398 structures.

399

400 In conclusion, this nationwide cohort study shows a globally low risk of VTE, hospitalized
401 bleeding and death after discharge, for patients given an anticoagulant for the prevention of
402 VTE following THR or TKR in a real-life setting, with a better benefit-risk ratio of DOAC
403 compared to LMWH, associated with cost savings.

404

405

Figure 1: Study flow chart

Figure 2: THR and TKR medical costs according to the societal perspective for DOAC and LMWH matched patients

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

	matched THR patients			matched TKR patients		
	DOAC n = 31 619	LMWH n = 31 619	Standardized difference	DOAC n = 15 720	LMWH n = 15 720	Standardized difference
Male, %	52.4	52.4	0.0	47.1	47.1	0.0
Age, mean (StD)	65.8 (10.7)	65.8 (10.7)	0.0	67.6 (8.9)	67.6 (8.9)	0.0
IMPROVE VTE risk score⁽¹⁾, %			-1.0			-2.1
1	27.1	27.1		19.9	19.9	
2	63.6	64.1		70.6	71.3	
>3	9.3	8.9		9.5	8.7	
IMPROVE bleeding risk score⁽¹⁾, %			-1.1			-0.4
< 2	23.0	23.1		18.6	18.3	
2 - 3.5	49.0	49.3		48.3	48.7	
4 - 6.5	27.5	27.1		32.6	32.6	

≥ 7	0.5	0.5		0.6	0.4	
Individual VTE or bleeding risk factors						
- Cancer history, %	11.9	11.0	-3.0	12.1	10.8	-4.2
- Active cancer ⁽²⁾ , %	8.8	8.2	-2.1	8.8	8.1	-2.5
- Atrial fibrillation, %	3.4	3.1	-2.1	3.9	3.1	-4.0
- Recent antithrombotic treatment history ⁽³⁾ , %	16.6	16.6	0.0	19.5	19.1	-1.0
- Oral contraception or HRT, %	10.9	10.5	-1.1	10.5	9.9	-1.9
- Antiplatelet agent ⁽⁴⁾ in the week after discharge, %	1.9	1.8	-1.1	2.0	1.9	-0.5
- ASA during follow-up, %	0.9	0.7	-2.5	1.2	0.8	-4.2
Index hospitalization						
- Category of hospital, %						
Teaching hospital	11.3	10.1	-3.9	8.1	6.9	-4.6
Other public hospital	12.4	12.8	1.4	10.5	11.0	1.8
Private hospital	76.3	77.0	1.7	81.5	82.1	1.7
- Duration, mean (SD)	7.0 (2.1)	7.0 (2.2)	0.9	7.7 (2.3)	7.7 (2.4)	1.5
- Hip, pelvis or leg fracture, %	1.9	2.0	0.8	0.3	0.2	-
- Bleeding diagnosis during hospitalization, %	1.3	1.1	-1.7	1.8	1.6	-1.3
Drug dispensing duration⁽⁵⁾ (days), mean (SD)	30.2 (5.9)	27.2 (7.6)	-	29.1 (6.9)	25.6 (8.3)	-

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

Table 2: Absolute and relative risk of VTE, bleeding and death between each DOAC and LMWH for THR and TKR matched patients

(1:x = LMWH:DOAC matched patient ratio)	Matched THR patients				Matched TKR patients				
	Population Size		Absolute risk		Relative risk [95% CI]	Population Size		Absolute risk	
	DOAC / LMWH	DOAC	LMWH	DOAC / LMWH		DOAC	LMWH	Relative risk [95% CI]	
	N / N	n (%)	n (%)	N / N	n (%)	n (%)			
VTE main diagnosis hospitalization									
All DOAC (1:1)	31 619 / 31 619	28 (0.9)	80 (2.5)	0.35 [0.23 - 0.54]	15 720 / 15 720	25 (1.6)	36 (2.3)	0.69 [0.42 - 1.16]	
Apixaban (1:6)	3 380 / 20 265	3 (0.9)	50 (2.5)	0.36 [0.11 - 1.15]	1 759 / 10 503	6 (3.4)	19 (1.8)	1.89 [0.75 - 4.72]	
Dabigatran (1:3)	7 098 / 21 286	9 (1.3)	47 (2.2)	0.57 [0.28 - 1.17]	3 554 / 10 648	7 (2.0)	29 (2.7)	0.72 [0.32 - 1.65]	
Rivaroxaban (1:1)	21 191 / 21 191	16 (0.8)	62 (2.9)	0.26 [0.15 - 0.45]	10 412 / 10 412	12 (1.2)	24 (2.3)	0.50 [0.25 - 1.00]	
Hospitalized⁽¹⁾ and non-hospitalized VTE									
All DOAC (1:1)	31 619 / 31 619	102 (3.2)	211 (6.7)	0.48 [0.38 - 0.61]	15 720 / 15 720	85 (5.4)	151 (9.6)	0.56 [0.43 - 0.73]	
Apixaban (1:6)	3 380 / 20 265	9 (2.7)	115 (5.7)	0.47 [0.24 - 0.92]	1 759 / 10 503	12 (6.8)	100 (9.5)	0.72 [0.39 - 1.30]	
Dabigatran (1:3)	7 098 / 21 286	15 (2.1)	134 (6.3)	0.34 [0.20 - 0.57]	3 554 / 10 648	14 (3.9)	95 (8.9)	0.44 [0.25 - 0.77]	
Rivaroxaban (1:1)	21 191 / 21 191	78 (3.7)	150 (7.1)	0.52 [0.40 - 0.68]	10 412 / 10 412	59 (5.7)	93 (8.9)	0.63 [0.46 - 0.88]	
Bleeding main diagnosis hospitalization									

All DOAC (1:1)	31 619 / 31 619	58 (1.8)	66 (2.1)	0.88 [0.62 - 1.25]	15 720 / 15 720	38 (2.4)	59 (3.8)	0.64 [0.43 - 0.97]
Apixaban (1:6)	3 380 / 20 265	4 (1.2)	38 (1.9)	0.63 [0.23 - 1.77]	1 759 / 10 503	5 (2.8)	32 (3.0)	0.93 [0.36 - 2.39]
Dabigatran (1:3)	7 098 / 21 286	12 (1.7)	49 (2.3)	0.73 [0.39 - 1.38]	3 554 / 10 648	3 (0.8)	45 (4.2)	0.20 [0.06 - 0.64]
Rivaroxaban (1:1)	21 191 / 21 191	42 (2.0)	45 (2.1)	0.93 [0.61 - 1.42]	10 412 / 10 412	30 (2.9)	38 (3.6)	0.79 [0.49 - 1.27]

Hospitalized⁽¹⁾ bleeding

All DOAC (1:1)	31 619 / 31 619	138 (4.4)	159 (5.0)	0.87 [0.69 - 1.09]	15 720 / 15 720	81 (5.2)	95 (6.0)	0.85 [0.63 - 1.15]
Apixaban (1:6)	3 380 / 20 265	10 (3.0)	84 (4.1)	0.71 [0.37 - 1.37]	1 759 / 10 503	7 (4.0)	55 (5.2)	0.76 [0.35 - 1.67]
Dabigatran (1:3)	7 098 / 21 286	31 (4.4)	101 (4.7)	0.92 [0.62 - 1.38]	3 554 / 10 648	13 (3.7)	70 (6.6)	0.56 [0.31 - 1.00]
Rivaroxaban (1:1)	21 191 / 21 191	97 (4.6)	114 (5.4)	0.85 [0.65 - 1.11]	10 412 / 10 412	62 (6.0)	59 (5.7)	1.05 [0.74 - 1.50]

Death

All DOAC (1:1)	31 619 / 31 619	23 (0.7)	34 (1.1)	0.68 [0.40 - 1.15]	15 720 / 15 720	9 (0.6)	13 (0.8)	0.69 [0.30 - 1.62]
Apixaban (1:6)	3 380 / 20 265	2 (0.6)	18 (0.9)	0.67 [0.15 - 2.87]	1 759 / 10 503	2 (1.1)	6 (0.6)	1.99 [0.40 - 9.86]
Dabigatran (1:3)	7 098 / 21 286	8 (1.1)	32 (1.5)	0.75 [0.35 - 1.63]	3 554 / 10 648	2 (0.6)	11 (1.0)	0.54 [0.12 - 2.46]
Rivaroxaban (1:1)	21 191 / 21 191	13 (0.6)	19 (0.9)	0.68 [0.34 - 1.39]	10 412 / 10 412		9 (0.9)	0.56 [0.19 - 1.66]

THR: Total Hip Replacement; TKR: Total Knee Replacement; DOAC: Direct Oral AntiCoagulant; LMWH: Low Molecular Weight Heparin; n: number of events; %: Absolute risk per 1000 persons; VTE: Venous Thromboembolic Event; (1) Hospitalization with main or associated diagnosis

THR and TKR hospitalisations from 1 Jan. 2013 to 30 Sept. 2014			
	ALL	THR	TKR
Population size, n	388 758	227 034	161 724
		THR^(a)	TKR^(a)
- Rehabilitation centre, (%) ^(a)		(33.5)	(46.6)
- Other institutionalization, (%) ^(a)		(6.0)	(6.5)
- No or other anticoagulant, ⁽¹⁾ (%) ^(a)		(9.3)	(7.2)
- Not eligible, ⁽²⁾ (%) ^(a)		(6.3)	(7.2)
- Died before discharge, (%) ^(a)		(1.5)	(0.4)
- Probable DRG error, ⁽³⁾ (%) ^(a)		(0.4)	(1.6)
Cohort	ALL	THR	TKR
LMWH, n	99 463	65 966	33 497
<i>Enoxaparin, n (%)^(b)</i>	<i>63 333 (63.7)</i>	<i>42 284 (64.1)</i>	<i>21 049 (62.8)</i>
<i>Tinzaparin, n (%)^(b)</i>	<i>32 245 (33.4)</i>	<i>21 714 (32.9)</i>	<i>11 531 (34.4)</i>
<i>Dalteparin, n (%)^(b)</i>	<i>2 812 (2.8)</i>	<i>1 919 (2.9)</i>	<i>893 (2.7)</i>
<i>Naldroparin, n (%)^(b)</i>	<i>73 (0.1)</i>	<i>49 (0.1)</i>	<i>24 (0.1)</i>
DOAC, n	47 418	31 680	15 738
<i>Rivaroxaban, n (%)^(c)</i>	<i>31 621 (66.7)</i>	<i>21 200 (66.9)</i>	<i>10 421 (66.2)</i>
<i>Dabigatran, n (%)^(c)</i>	<i>10 657 (22.5)</i>	<i>7 099 (22.4)</i>	<i>3 558 (22.6)</i>
<i>Apixaban, n (%)^(c)</i>	<i>5 140 (10.8)</i>	<i>3 381 (10.7)</i>	<i>1 759 (11.2)</i>
1:1 Matched patients	ALL	THR	TKR
LMWH, n (%)^(b)	47 339 (47.6)	31 619 (47.9)	15 720 (46.9)
DOAC, n (%)^(c)	47 339 (99.8)	31 619 (99.9)	15 720 (99.8)
<p>(a) % of all THR or TKR; (b) % of all LMWH cohort patients; (c) % of all DOAC cohort patients; (1) No anticoagulant dispensing found or unfractionated heparin, fondaparinux or vitamin-K antagonist or anticoagulant associations first within one week after discharge; (2) Not in the reference directory or < 18 years, database history < 3 years, database follow-up < 3 months, other than teaching, general or private hospitals; (3) discrepancy between Diagnosis Related Group and primary diagnosis for THR or TKR. THR = Total Hip Replacement; TKR = Total Knee Replacement; DOAC = Direct Oral Anticoagulant; LMWH = Low molecular weight Heparin</p>			

Figure 1: Study flow chart

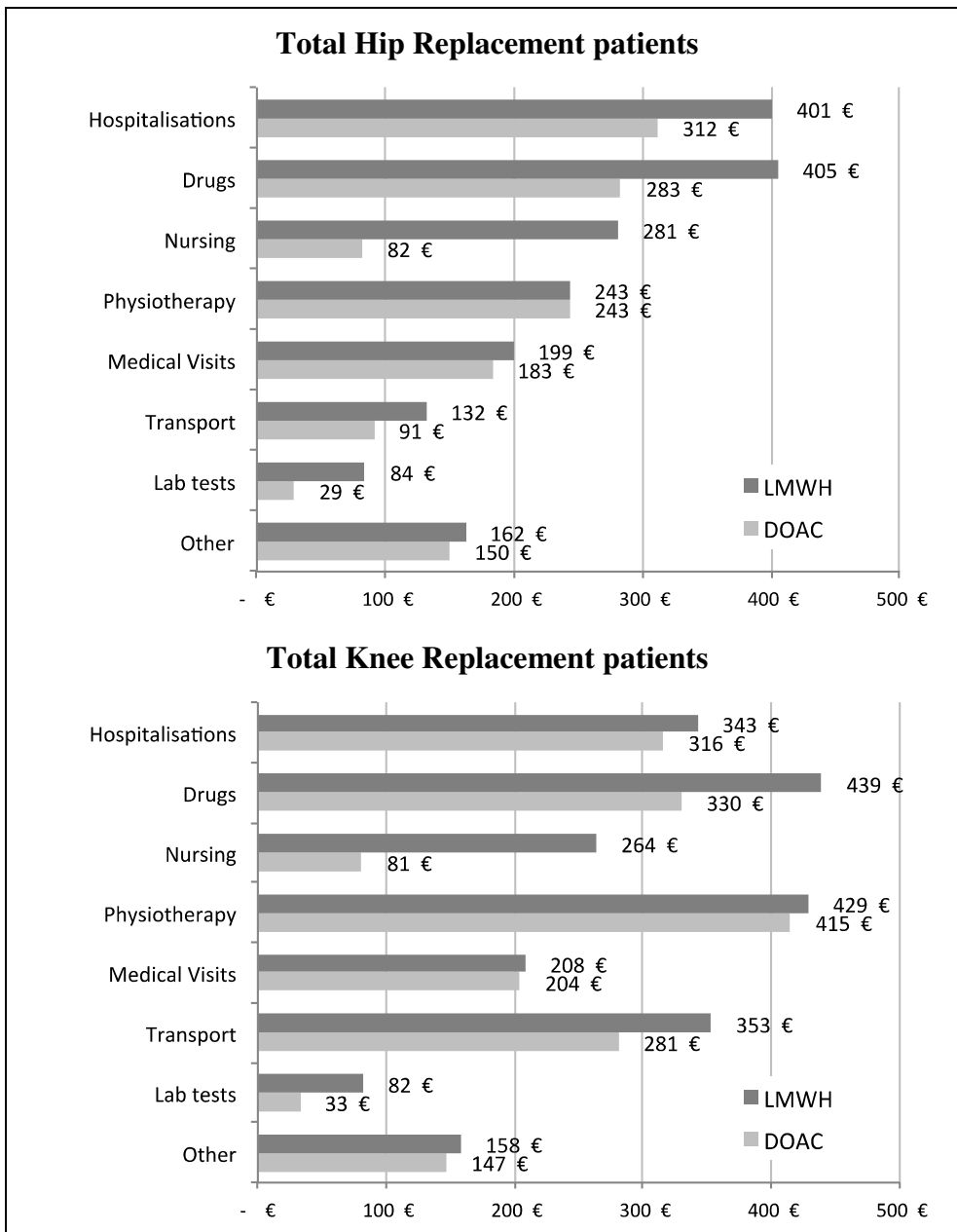


Figure 2: THR and TKR medical costs according to the collective perspective for DOAC and LMWH matched patients
 DOAC = Direct Oral AntiCoagulant; LMWH = Low Molecular Weight Heparin.

