SSVQ Société des sciences vasculaires du Québec
Chef de file en santé vasculaire.

# Thromboprophylaxie orthopédique en 2022

Présenté par Dr Benoit Côté

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# Divulgation de renseignements financiers

- J'ai obtenu des honoraires de conférencier de la part de **BMS, Pfizer** et **Bayer**
- J'ai obtenu des honoraires pour des conseils consultatifs de **BMS/Pfizer, Servier** et **LEOpharma**

- *J'avais entièrement droit de regard sur le contenu de la présentation et tiens à préciser que cette dernière peut renfermer des renseignements qui ne concordent pas avec les monographies approuvées au Canada de certains produits.*

# Objectifs - Plan

- Revoir les recommandations actuelles en thromboprophylaxie de PTG et PTH
- Survoler les données scientifiques supportant les recommandations actuelles
- Introduire les avenues futures en thromboprophylaxie orthopédique

# La problématique

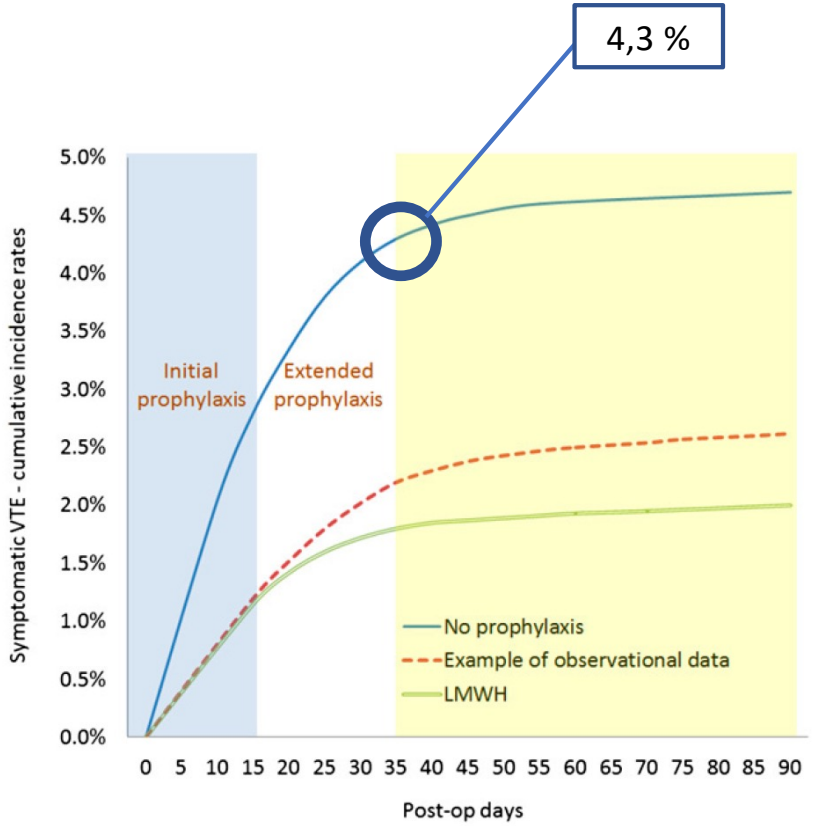



**Table 2—*[Section 1.3.1] Estimated Nonfatal, Symptomatic VTE Rates After Major Orthopedic Surgery***

| | Initial Prophylaxis, Postoperative Days 0-14 | Extended Prophylaxis, Postoperative Days 15-35 | Cumulative, Postoperative Days 0-35 |
|---|---|---|---|
| No prophylaxis | VTE 2.80% (PE 1.00%, DVT 1.80%) | VTE 1.50% (PE 0.50%, DVT 1.00%) | VTE 4.3% (PE 1.50%, DVT 2.80%) |
| LMWH | VTE 1.15% (PE 0.35%, DVT 0.80%) | VTE 0.65% (PE 0.20%, DVT 0.45%) | VTE 1.8% (PE 0.55%, DVT 1.25%) |

See Table 1 legend for expansion of abbreviations.

Falc-Ytter Y. et al. Chest 2012;141(2)(Suppl);e278S-e325S

# Thromboprophylaxie orthopédique

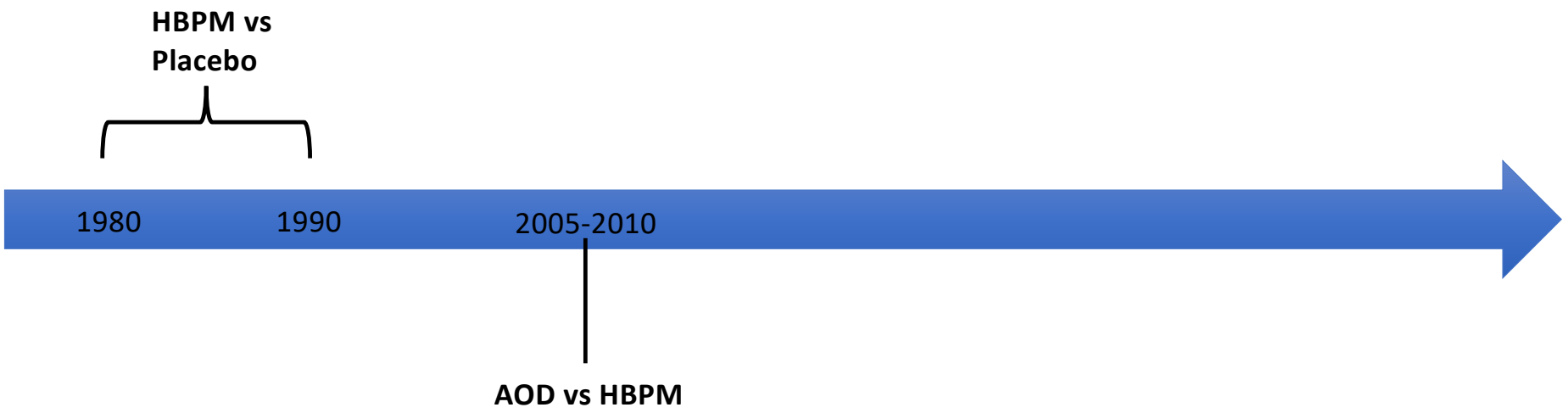
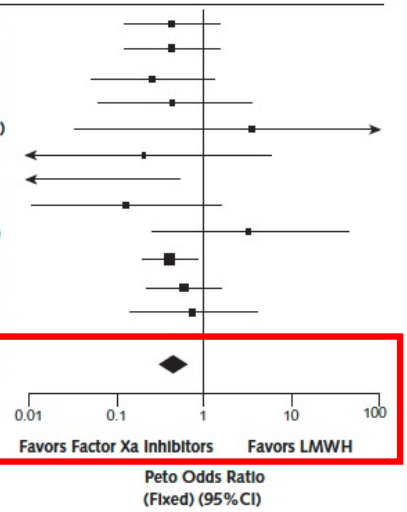


*Figure 3.* **Symptomatic deep venous thrombosis up to 5 weeks with oral direct factor Xa inhibitors versus LMWH.**

| Study, Year (Reference) or Subgroup | Factor Xa Inhibitors Events | Factor Xa Inhibitors Total | LMWH Events | LMWH Total | Weight, % | Peto Odds Ratio (Fixed) (95% CI) |
|---|---|---|---|---|---|---|
| ADVANCE-1 | 3 | 1599 | 7 | 1596 | 11.6 | 0.45 (0.13–1.55) |
| ADVANCE-2 | 3 | 1528 | 7 | 1529 | 11.6 | 0.45 (0.13–1.55) |
| ADVANCE-3 | 1 | 2708 | 5 | 2699 | 6.9 | 0.26 (0.05–1.30) |
| APROPOS | 3 | 638 | 2 | 218 | 4.4 | 0.46 (0.06–3.48) |
| Eriksson et al, 2007 (41) | 1 | 359 | 0 | 107 | 0.8 | 3.66 (0.03–386.89) |
| EXPERT | 1 | 135 | 1 | 40 | 1.6 | 0.21 (0.01–5.82) |
| ODIXa 1 | 0 | 511 | 1 | 107 | 0.7 | 0.00 (0.00–0.55) |
| ODIXa 2 | 2 | 296 | 2 | 70 | 2.8 | 0.13 (0.01–1.63) |
| ONYX-2 | 4 | 581 | 0 | 127 | 2.7 | 3.40 (0.26–43.97) |
| RECORD3 | 8 | 1201 | 20 | 1217 | 32.1 | 0.43 (0.20–0.90) |
| RECORD4 | 6 | 1526 | 10 | 1508 | 18.4 | 0.60 (0.22–1.60) |
| Weitz et al, 2010 (29) | 9 | 621 | 2 | 109 | 6.4 | 0.77 (0.15–4.10) |
| Total (95% CI) | | 11 703 | | 9327 | 100.0 | 0.46 (0.30–0.70) |
| Total events | 41 | | 57 | | | |
| Heterogeneity: chi-square = 8.99, $I^2$ = 0% | | | | | | |
| Test for overall effect: $Z$ = 3.60 ($P$ = 0.0003) | | | | | | |




ADVANCE = Apixaban Dose Orally vs. Anticoagulant with Enoxaparin; APROPOS = Apixaban Prophylaxis in Patients undergoing total knee replacement Surgery; EXPERT = A randomized evaluation of betrixaban, an oral factor Xa inhibitor, for prevention of thromboembolic events after total knee replacement; LMWH = low-molecular-weight heparin; ODIXa = Oral DIrect factor Xa inhibitor; ONYX = Oral direct iNhibition by YM150 of factor Xa; RECORD = Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism.

Saignement majeur : *OR, 1.27 [CI, 0.98 to 1.65]; $I^2$ 55%)*

Neumann I. et al. *Ann Intern Med. 2012;156:710-719.*

# Quelles sont les recommandations actuelles et leurs évidences ?

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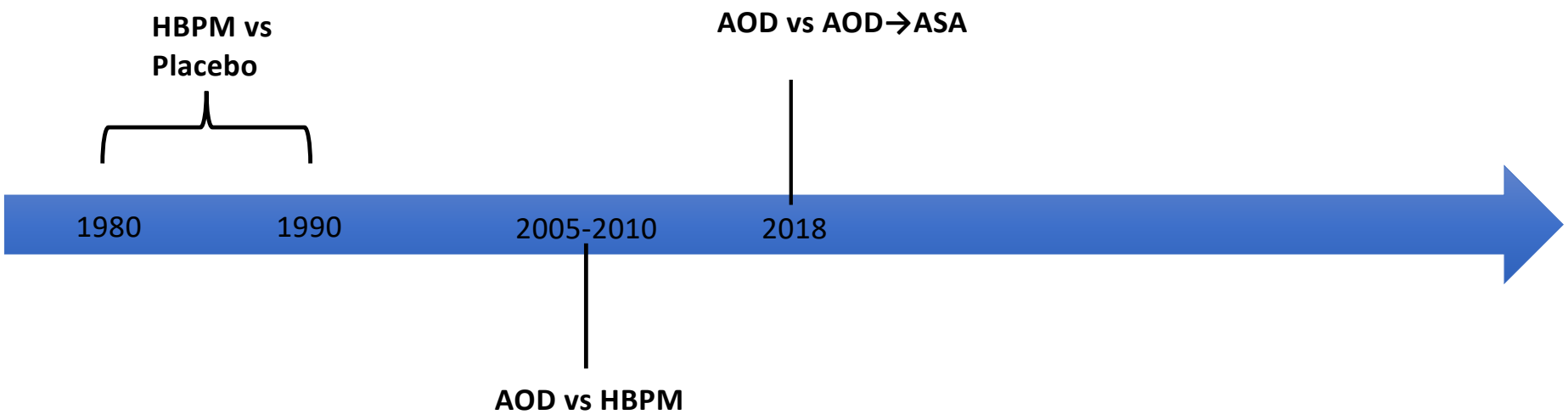
# American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients

***Orthopedic surgery***

RECOMMENDATIONS 9 TO 13. For patients undergoing total hip arthroplasty or total knee arthroplasty, the ASH guideline panel *suggests* using aspirin (ASA) or anticoagulants (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). When anticoagulants are used, the panel *suggests* using direct oral anticoagulants (DOACs) over low-molecular-weight heparin (LMWH) (conditional recommendation based on moderate certainty in the evidence of effects ⊕⊕⊕◯); the panel *suggests* using any of the DOACs approved for use (conditional recommendation based on low certainty in the evidence of effects ⊕⊕◯◯). If a DOAC is not used, the panel *suggests* using LMWH rather than warfarin (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯) and *recommends* LMWH rather than unfractionated heparin (UFH) (strong recommendation based on moderate certainty in the evidence of effects ⊕⊕⊕◯).

# Thromboprophylaxie orthopédique



The NEW ENGLAND JOURNAL of MEDICINE
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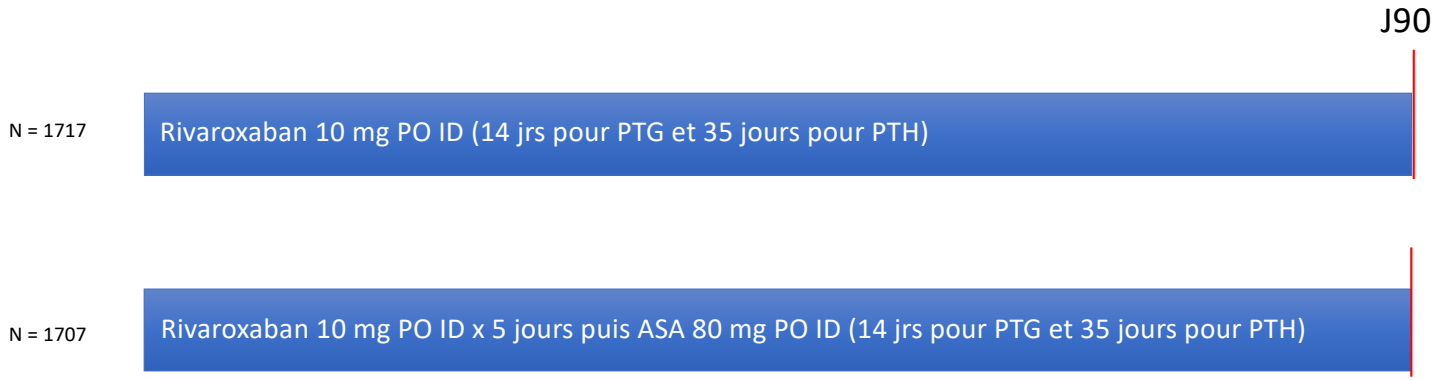
# Aspirin or Rivaroxaban for VTE Prophylaxis after Hip or Knee Arthroplasty

Étude canadienne en double aveugle, randomisée, contrôlée

Étude de non-infériorité



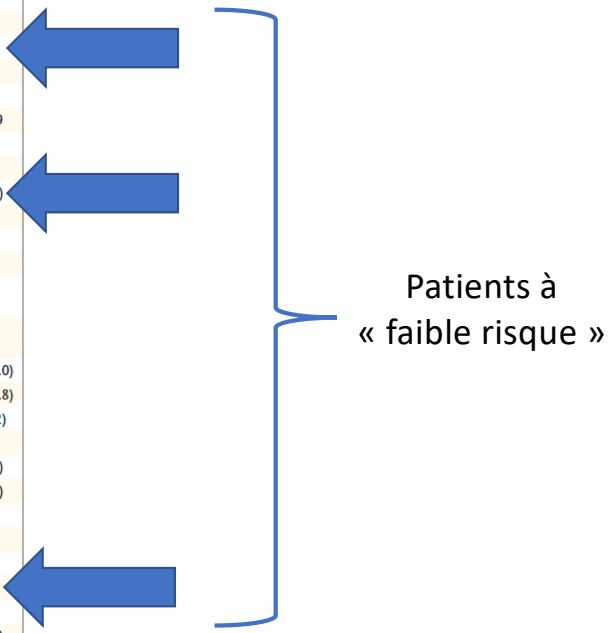

**Outcome 1°** :
TEV proximale
**symptomatique (TVP et EP)**

*Anderson D.R et Al. N Engl J Med 2018;378:699-707.*

**Table 1. Characteristics of the Patients at Baseline, According to Surgical Subgroup.***

| Characteristic | Total Hip Arthroplasty | | Total Knee Arthroplasty | | All Patients | |
|---|---|---|---|---|---|---|
| | Rivaroxaban (N=902) | Aspirin (N=902) | Rivaroxaban (N=815) | Aspirin (N=805) | Rivaroxaban (N=1717) | Aspirin (N=1707) |
| Age — yr | 60.9±11.0 | 61.3±11.1 | 64.7±8.4 | 64.6±8.7 | 62.7±10.1 | 62.9±10.1 |
| Male sex — no. (%) | 480 (53.2) | 486 (53.9) | 353 (43.3) | 318 (39.5) | 833 (48.5) | 804 (47.1) |
| Body-mass index† | 29.4±5.8 | 29.4±6.0 | 32.7±6.8 | 33.0±7.2 | 31.0±6.6 | 31.1±6.8 |
| Risk factors — no. (%) | | | | | | |
| Previous venous thromboembolism | 22 (2.4) | 20 (2.2) | 22 (2.7) | 17 (2.1) | 44 (2.6) | 37 (2.2) |
| Previous surgery | 28 (3.1) | 30 (3.3) | 18 (2.2) | 28 (3.5) | 46 (2.7) | 58 (3.4) |
| Cancer | 19 (2.1) | 17 (1.9) | 19 (2.3) | 25 (3.1) | 38 (2.2) | 42 (2.5) |
| Current smoker | 86 (9.5) | 83 (9.2) | 71 (8.7) | 79 (9.8) | 157 (9.1) | 162 (9.5) |
| Hemoglobin — g/liter | 140.4±12.5 | 140.2±13.0 | 138.2±12.8 | 138.0±12.8 | 139.4±12.7 | 139.2±12.9 |
| Mean platelet count per $mm^3$ | 241,200 | 238,700 | 240,700 | 244,100 | 240,900 | 241,200 |
| Type of surgery — no. (%) | | | | | | |
| Primary | 802 (88.9) | 809 (89.7) | 770 (94.5) | 760 (94.4) | 1572 (91.6) | 1569 (91.9) |
| Revision | 64 (7.1) | 52 (5.8) | 44 (5.4) | 42 (5.2) | 108 (6.3) | 94 (5.5) |
| Resurfacing | 35 (3.9) | 41 (4.5) | NA | NA | 35 (2.0) | 41 (2.4) |
| Other | 1 (0.1) | 0 | 1 (0.1) | 3 (0.4) | 2 (0.1) | 3 (0.2) |
| Use of tranexamic acid — no./total no. (%) | 478/898 (53.2) | 470/901 (52.2) | 456/812 (56.2) | 455/802 (56.7) | 934/1710 (54.6) | 925/1703 (54.3) |
| Postoperative mechanical compression — no./total no. (%) | | | | | | |
| Pneumatic compression | 93/155 (60.0) | 94/162 (58.0) | 50/119 (42.0) | 44/114 (38.6) | 143/274 (52.2) | 138/276 (50.0) |
| Graduated stockings | 45/155 (29.0) | 53/162 (32.7) | 62/119 (52.1) | 65/114 (57.0) | 107/274 (39.1) | 118/276 (42.8) |
| Both | 17/155 (11.0) | 15/162 (9.3) | 7/119 (5.9) | 5/114 (4.4) | 24/274 (8.8) | 20/276 (7.2) |
| Anesthetic — no. (%) | | | | | | |
| General | 263 (29.2) | 288 (31.9) | 214 (26.3) | 205 (25.5) | 477 (27.8) | 493 (28.9) |
| Regional | 628 (69.6) | 605 (67.1) | 597 (73.3) | 596 (74.0) | 1225 (71.3) | 1201 (70.4) |
| Both | 11 (1.2) | 9 (1.0) | 4 (0.5) | 4 (0.5) | 15 (0.9) | 13 (0.8) |
| Time in operating room — hr | 1.4±0.6 | 1.4±0.6 | 1.4±0.5 | 1.4±0.5 | 1.4±0.6 | 1.4±0.6 |
| Estimated blood loss — ml | 369±270 | 374±295 | 227±174 | 234±172 | 307±244 | 314±259 |
| Length of hospital stay — days | 3.3±1.6 | 3.4±1.9 | 3.6±1.6 | 3.6±1.5 | 3.4±1.6 | 3.5±1.8 |
| Surgical approach — no. (%) | | | | | | |
| Direct lateral | 425 (47.1) | 421 (46.7) | NA | NA | 425 (24.8) | 421 (24.7) |
| Posterior | 386 (42.8) | 391 (43.3) | NA | NA | 386 (22.5) | 391 (22.9) |
| Anterolateral | 49 (5.4) | 50 (5.5) | NA | NA | 49 (2.9) | 50 (2.9) |
| Anterior | 42 (4.7) | 40 (4.4) | NA | NA | 42 (2.4) | 40 (2.3) |
| Anterior longitudinal midline | NA | NA | 815 (100) | 805 (100) | 815 (47.5) | 805 (47.2) |
| Prosthesis — no. (%) | | | | | | |
| Cemented | 57 (6.3) | 49 (5.4) | 742 (91.0) | 727 (90.3) | 799 (46.5) | 776 (45.5) |
| Hybrid | 56 (6.2) | 55 (6.1) | 47 (5.8) | 55 (6.8) | 103 (6.0) | 110 (6.4) |
| Noncemented | 789 (87.5) | 798 (88.5) | 25 (3.1) | 23 (2.9) | 814 (47.4) | 821 (48.1) |
| Missing data | 0 | 0 | 1 (0.1) | 0 | 1 (0.1) | 0 |

* Plus–minus values are means ±SD. None of the between-group comparisons were significant at baseline. NA denotes not applicable.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.




*Anderson D.R et Al. N Engl J Med 2018;378:699-707.*

**Table 2. Primary Effectiveness and Safety Outcomes.**

| Outcome | Rivaroxaban (N=1717) | Aspirin (N=1707) | P Value |
|---|---|---|---|
| | *no. of patients (%)* | | |
| Venous thromboembolism | 12 (0.70) | 11 (0.64) | 0.84* |
| Pulmonary embolism | 6 (0.35) | 5 (0.29) | |
| Proximal deep-vein thrombosis | 4 (0.23) | 4 (0.23) | |
| Pulmonary embolism and proximal deep-vein thrombosis | 2 (0.12) | 2 (0.12) | |
| Major bleeding | 5 (0.29) | 8 (0.47) | 0.42 |
| Any bleeding† | 17 (0.99) | 22 (1.29) | 0.43 |

* P<0.001 for noninferiority, as defined by the upper boundary of the 95% confidence interval for the absolute between-group difference.
† This category includes major bleeding and clinically relevant nonmajor bleeding.

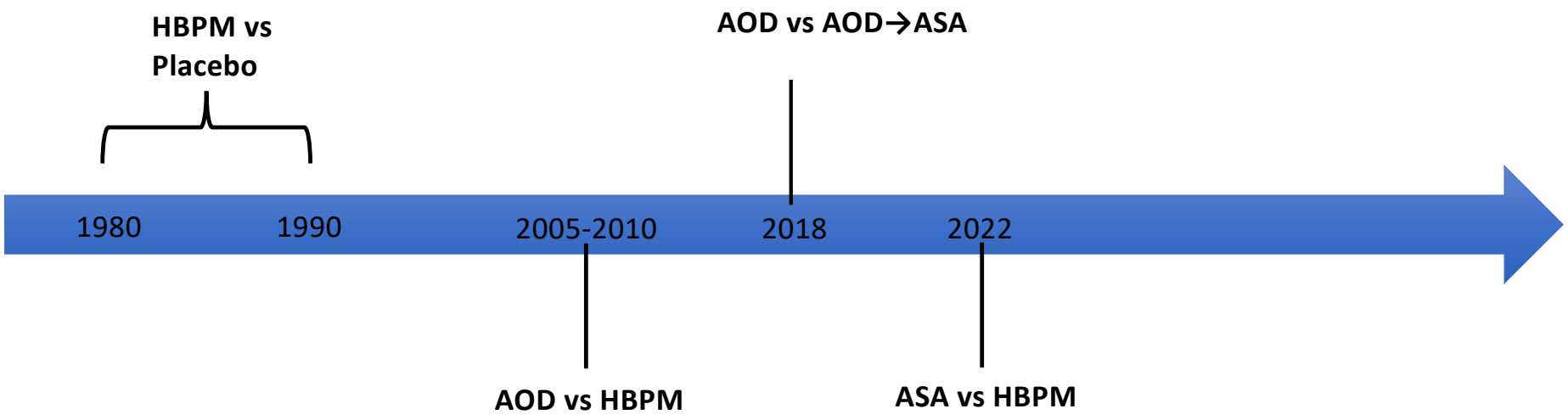
**Table 3. Primary Effectiveness and Safety Outcomes, According to Surgical Procedure.**

| Outcome | Total Hip Arthroplasty | | | Total Knee Arthroplasty | | |
|---|---|---|---|---|---|---|
| | Rivaroxaban (N=902) | Aspirin (N=902) | P Value | Rivaroxaban (N=815) | Aspirin (N=805) | P Value |
| | *no. (%)* | | | *no. (%)* | | |
| Venous thromboembolism | 5 (0.55) | 4 (0.44) | 1.00* | 7 (0.86) | 7 (0.87) | 1.00† |
| Pulmonary embolism | 2 (0.22) | 2 (0.22) | | 4 (0.49) | 3 (0.37) | |
| Proximal deep-vein thrombosis | 1 (0.11) | 1 (0.11) | | 3 (0.37) | 3 (0.37) | |
| Pulmonary embolism and proximal deep-vein thrombosis | 2 (0.22) | 1 (0.11) | | 0 | 1 (0.12) | |
| Major bleeding | 3 (0.33) | 3 (0.33) | 1.00 | 2 (0.25) | 5 (0.62) | 0.29 |
| All bleeding‡ | 7 (0.78) | 11 (1.22) | 0.48 | 10 (1.23) | 11 (1.37) | 0.83 |

* P=0.001 for noninferiority.
† P=0.03 for noninferiority.
‡ This category includes major bleeding and clinically relevant nonmajor bleeding.

*Anderson D.R et Al. N Engl J Med 2018;378:699-707.*

# Thromboprophylaxie orthopédique



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# American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients

## *Orthopedic surgery*

RECOMMENDATIONS 9 TO 13. For patients undergoing total hip arthroplasty or total knee arthroplasty, the ASH guideline panel *suggests* using aspirin (ASA) or anticoagulants (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯). When anticoagulants are used, the panel *suggests* using direct oral anticoagulants (DOACs) over low-molecular-weight heparin (LMWH) (conditional recommendation based on moderate certainty in the evidence of effects ⊕⊕⊕◯); the panel *suggests* using any of the DOACs approved for use (conditional recommendation based on low certainty in the evidence of effects ⊕⊕◯◯). If a DOAC is not used, the panel *suggests* using LMWH rather than warfarin (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯) and *recommends* LMWH rather than unfractionated heparin (UFH) (strong recommendation based on moderate certainty in the evidence of effects ⊕⊕⊕◯).

## Aspirin compared with anticoagulants:

| Outcomes | Relative effect (95% CI) | Anticipated absolute effects (95% CI) | |
|---|---|---|---|
| | | *Risk with **ANTICOAGULANTS*** | *Risk difference with **ASPIRIN*** |
| Mortality | **RR 2.32** (0.15 to 36.90) | 1 per 1,000 | **1 more death per 1,000** (1 fewer to 33 more) |
| Symptomatic PE | **RR 1.49** (0.37 to 6.09) | 6 per 1,000 | **3 more PE per 1,000** (4 fewer to 29 more) |
| Symptomatic proximal DVT | **RR 1.49** (0.51 to 4.34) | 6 per 1,000 | **3 more DVT per 1,000** (3 fewer to 30 more) |
| Major bleeding | **RR 2.63** (0.64 to 10.79) | 4 per 1,000 | **6 more bleeds per 1,000** (1 fewer to 35 more) |

***Certainty in the evidence of effects.*** We rated the overall certainty in the evidence of effects as very low based on the lowest certainty in the evidence for the critical outcomes, downgrading for study limitations, indirectness, and imprecision.

***Summary of the evidence.*** We found 7 RCTs that compared the use of ASA vs anticoagulants for patients undergoing total hip arthroplasty or total knee arthroplasty.[193-199] Additionally, we identified 2 trials comparing ASA with LMWH in total hip arthroplasty patients[200] and ASA with DOAC in total hip arthroplasty or total knee arthroplasty patients,[201] in which all participants received a 10-day period of LMWH or a 5-day period of DOACs, respectively, prior to randomization. The trials were reviewed by the panel but were not included in the main meta-analysis because of differences in the comparator groups. Of the 7 studies included in the analysis, 2 studies compared ASA with UFH,[193,195] 4 studies compared ASA with LMWH,[194,196,198,199] and 2 studies compared ASA with oral anticoagulants.[197,199] All 7 studies reported the outcomes of mortality and PE,[193-199] 6 studies reported on proximal and distal DVTs,[195-199] and 5 studies reported on major bleeding.[194-196,198,199] We found no studies addressing the outcome of reoperation.

EPCAT II non inclus dans les analyses de l'ASH et pas de recommandation sur le régime hybride

# Recommandation d'une société orthopédique

**3 - What is the most optimal VTE prophylaxis following TKA/THA?**

**Response/Recommendation:** Low-dose aspirin (ASA) is currently the most effective and safest method of prophylaxis against venous thromboembolism (VTE) in patients undergoing total joint arthroplasty (TJA). We recommend the use of low-dose ASA as the primary method of VTE prophylaxis in all patients undergoing TJA, including moderate-to high-risk patients.

**Strength of Recommendation**: Strong.

**Delegates vote**: Agree 76.92% Disagree 19.66% Abstain 3.42% (Strong Consensus).

*J Bone Joint Surg Am. 2022;104 Suppl 1:180-231*

# Une tendance forte (américaine)

| | Mécanique | ASA +/- Mécanique | HBPM +/- Mécanique | AVK +/- Mécanique | Anti Xa +/- Mécanique |
|---|---|---|---|---|---|
| PTG (n = 303) | 0 % | 97 % | 1 % | 0 % | 2 % |
| PTH (n = 366) | 0 % | 95 % | 3 % | 0 % | 2 % |

*The Journal of Arthroplasty 36 (2021) S40eS44*

JAMA | Original Investigation

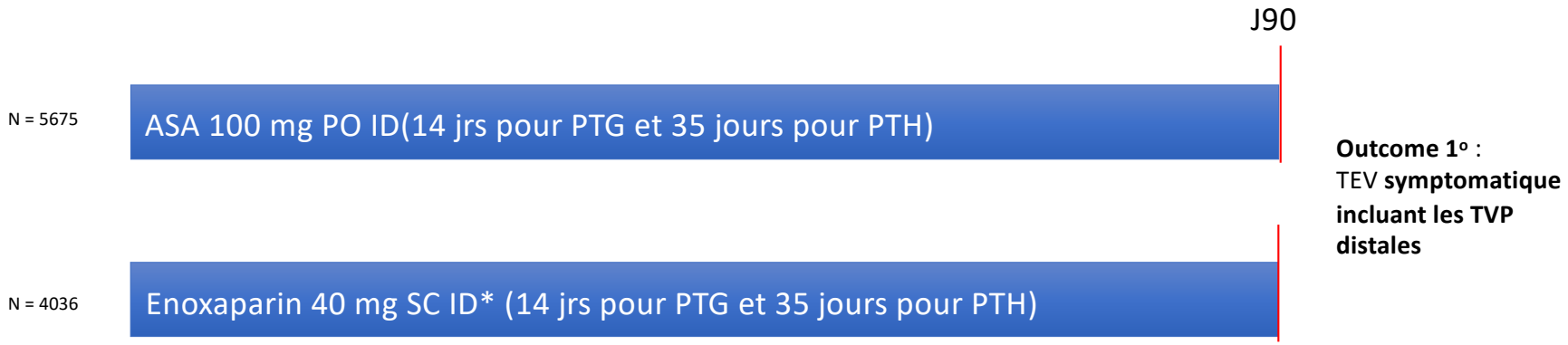
# Effect of Aspirin vs Enoxaparin on Symptomatic Venous Thromboembolism in Patients Undergoing Hip or Knee Arthroplasty

## The CRISTAL Randomized Trial

CRISTAL Study Group

Cluster-randomized, crossover study sur 31 sites australiens

Étude de non-infériorité




* Dose réduite 20mg SC ID si poids < 50 KG ou clairance < 30 cc/min

*CRISTAL Study Group. JAMA. 2022;328(8):719-727.*

**Table 1. Baseline Patient Characteristics**

| Characteristics | Aspirin (n = 5675) | Enoxaparin (n = 4036) |
|---|---|---|
| Age, median (IQR), y | 67.0 (61.0-74.0) | 68.0 (61.0-74.0) |
| Body mass index, median (IQR)[a] | 30.5 (26.9-35.1) | 30.6 (26.9-34.9) |
| Sex, No. (%) | | |
| Female | 3208 (56.5) | 2303 (57.1) |
| Male | 2467 (43.5) | 1733 (42.9) |
| American Society of Anesthesiologists classification, No. (%)[b] | | |
| I | 315 (5.6) | 201 (5.0) |
| II | 3219 (56.9) | 2221 (55.1) |
| III | 2074 (36.7) | 1582 (39.2) |
| IV | 47 (0.8) | 29 (0.7) |
| Previous deep venous thrombosis or pulmonary embolism, No. (%) | 276 (5.2) | 240 (6.3) |
| Preoperative antiplatelet therapy, No. (%) | | |
| Aspirin | 817 (15.4) | 584 (15.2) |
| Other single antiplatelet agent | 67 (1.3) | 50 (1.3) |
| Other agent (unspecified) | 197 (3.7) | 133 (3.5) |
| Joint replacement, No. (%) | | |
| Unilateral total knee arthroplasty | 2973 (52.4) | 2113 (52.4) |
| Unilateral total hip arthroplasty | 2066 (36.4) | 1494 (37.0) |
| Bilateral total knee arthroplasty | 547 (9.6) | 385 (9.5) |
| Bilateral total hip arthroplasty | 89 (1.6) | 44 (1.1) |
| Prosthesis, No. (%) | | |
| Cemented | 2781 (49.0) | 2067 (51.2) |
| Hybrid | 1454 (25.6) | 1088 (27.0) |
| Uncemented | 1440 (25.4) | 881 (21.8) |

[a] Calculated as weight in kilograms divided by height in meters squared.

[b] As determined by anesthesiologist on the day of surgery. This classification assesses and communicates a patient's preanesthesia medical comorbidities and ranges from I to VI, with I being healthy and VI being brain death.

*CRISTAL Study Group. JAMA. 2022;328(8):719-727.*

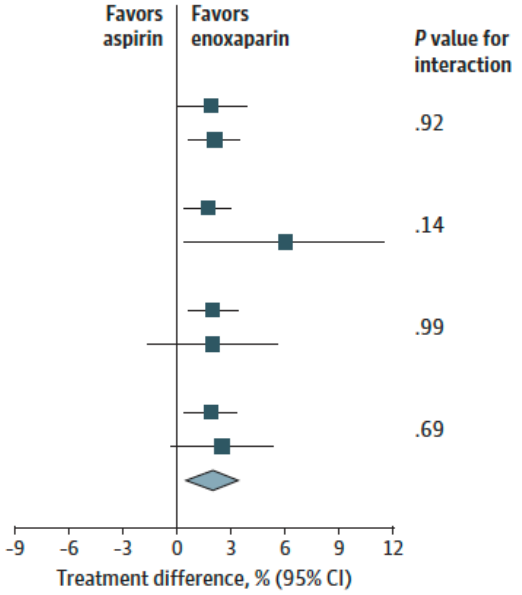
**Table 2. Primary and Secondary Outcomes for Patients Undergoing Primary Total Hip or Knee Arthroplasty for a Diagnosis of Osteoarthritis Who Were Eligible to Receive the Study Drug**

| Outcomes | No./total (%) | | Estimated treatment difference, % (95% CI)[a] | *P* value[b] |
|---|---|---|---|---|
| | Aspirin (n = 5416) | Enoxaparin (n = 3787) | | |
| **Primary outcome** | | | | |
| Any symptomatic venous thromboembolism within 90 d | 187/5416 (3.5) | 69/3787 (1.8) | 1.97 (0.54 to 3.41)[c] | .007 |
| **Components of primary outcome[d]** | | | | |
| Pulmonary embolism within 90 d | 58/5416 (1.1) | 21/3787 (0.6) | 0.44 (−0.19 to 1.08) | .17 |
| Any deep venous thrombosis within 90 d | 140/5416 (2.6) | 50/3787 (1.3) | 1.61 (0.54 to 2.68) | .003 |
| Both pulmonary embolism and deep venous thrombosis within 90 d | 11/5416 (0.2) | 2/3787 (0.1) | 0.10 (−0.10 to −0.30) | .32 |
| Above-knee deep venous thrombosis within 90 d[e] | 12/5415 (0.2) | 6/3787 (0.2) | 0.06 (−0.11 to 0.23) | .49 |
| Below-knee deep venous thrombosis within 90 d | 129/5415 (2.4) | 45/3787 (1.2) | 1.49 (0.48 to 2.50) | .004 |
| **Secondary outcomes** | | | | |
| Death within 90 d[f] | 4/5675 (0.1) | 2/4036 (0.1) | 0.05 (−0.05 to 0.15) | .36 |
| Major bleeding within 90 d | 17/5401 (0.3) | 15/3779 (0.4) | −0.05 (−0.35 to 0.25) | .75 |
| Readmission within 90 d | 130/5403 (2.4) | 85/3782 (2.3) | 0.6 (−0.19 to 1.39) | .13 |
| Reoperation within 90 d | 116/5412 (2.1) | 73/3787 (1.9) | 0.67 (−0.12 to 1.46) | .10 |
| Reoperation within 6 mo | 175/5086 (3.4) | 120/3535 (3.4) | 0.16 (−0.82 to 1.14) | .75 |
| Drug adherence | 521/614 (85) | 491/569 (86) | −0.99 (−0.91 to 1.08) | .85 |

*CRISTAL Study Group. JAMA. 2022;328(8):719-727.*

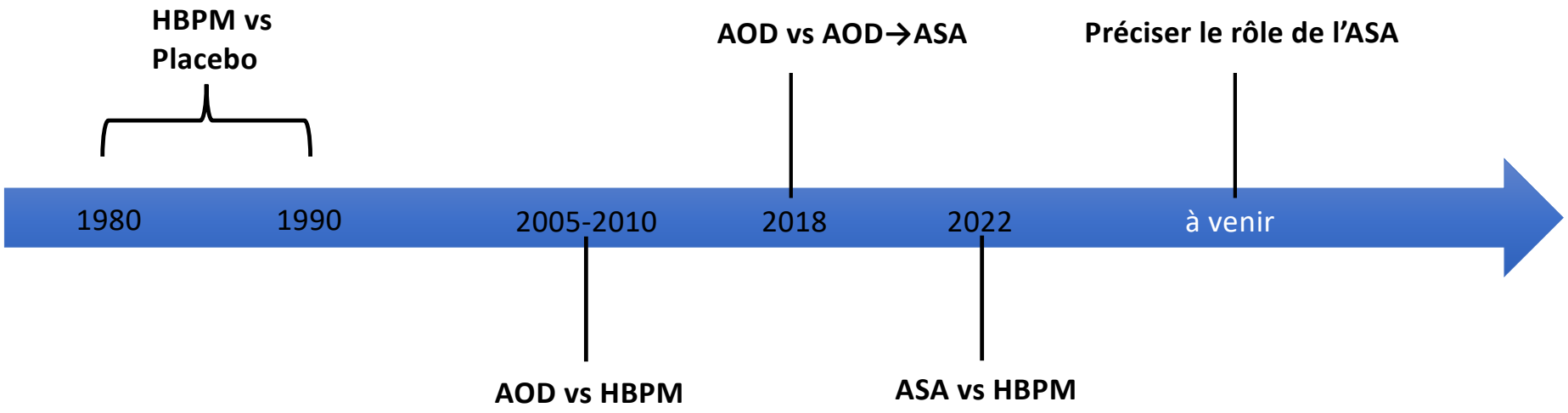
**Figure 2. Subgroup Analyses of the Primary Outcome of Symptomatic Venous Thromboembolism (Deep Venous Thrombosis or Pulmonary Embolism) Within 90 Days**

| Subgroup | No./total No. (%) | | Unadjusted treatment difference, % (95% CI) | *P* value for interaction |
|---|---|---|---|---|
| | Aspirin | Enoxaparin | | |
| Joint replacement | | | | |
| Total hip arthroplasty | 42/2068 (2.0) | 7/1430 (0.5) | 1.9 (0.0 to 3.9) | .92 |
| Total knee arthroplasty | 145/3348 (4.3) | 62/2357 (2.6) | 2.1 (0.6 to 3.5) | |
| History of venous thromboembolism | | | | |
| No | 155/4826 (3.2) | 60/3379 (1.8) | 1.7 (0.4 to 3.0) | .14 |
| Yes | 23/270 (8.5) | 6/228 (2.6) | 6.0 (0.4 to 11.5) | |
| Bilateral arthroplasty | | | | |
| No | 161/4802 (3.4) | 56/3378 (1.7) | 2.0 (0.6 to 3.4) | .99 |
| Yes | 26/614 (4.2) | 13/409 (3.2) | 2.0 (−1.6 to 5.6) | |
| Preoperative single antiplatelet use | | | | |
| No | 132/4070 (3.2) | 45/2882 (1.6) | 1.9 (0.4 to 3.3) | .69 |
| Yes | 47/1031 (4.6) | 21/725 (2.9) | 2.5 (−0.3 to 5.3) | |
| All patients | 187/5416 (3.5) | 69/3787 (1.8) | 2.0 (0.5 to 3.4) | |




*CRISTAL Study Group. JAMA. 2022;328(8):719-727.*

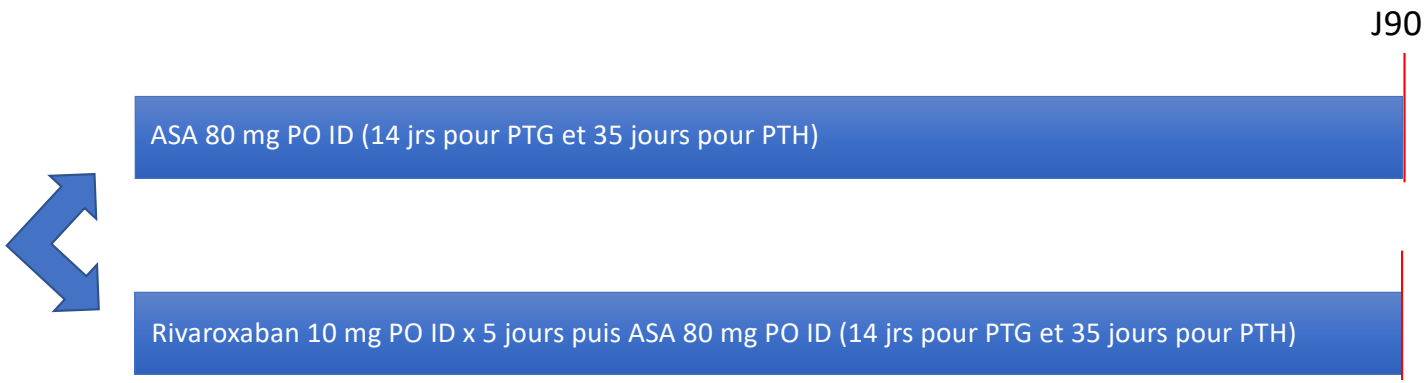
# Thromboprophylaxie orthopédique



# À venir

CANVECTOR

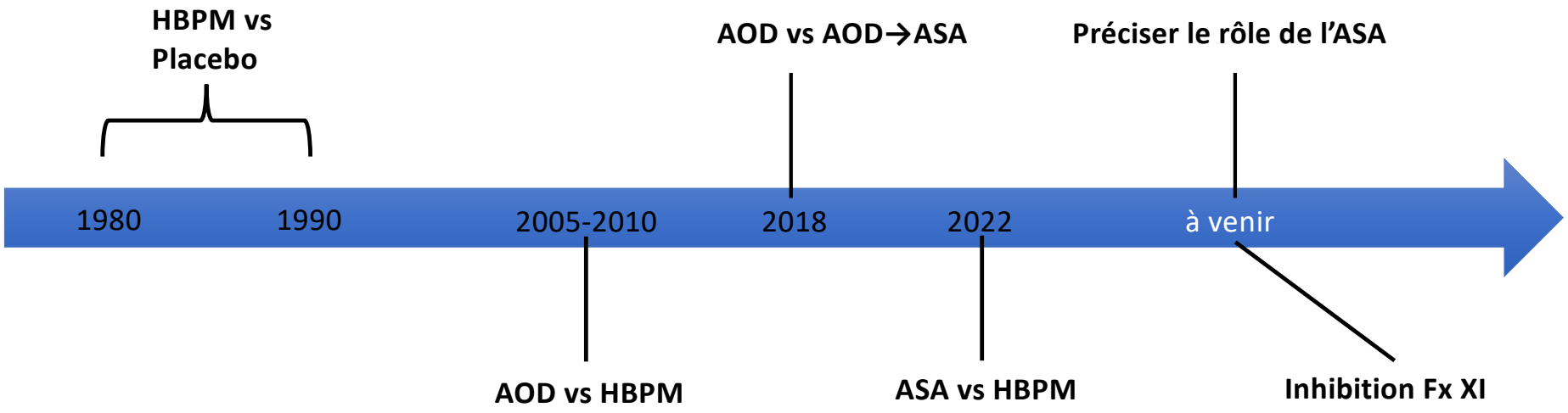
## EPCAT III : Patient avec PTH ou PTG




**Outcome 1o** :
TEV proximaled **symptomatique** et saignement (majeur et cliniquement significatif)

Y a-t-il d’autres avenues à venir pour nos patients ?

# Thromboprophylaxie orthopédique



# Découpler l'hémostase et la formation de thrombus

Rôle mineur

Rôle majeur

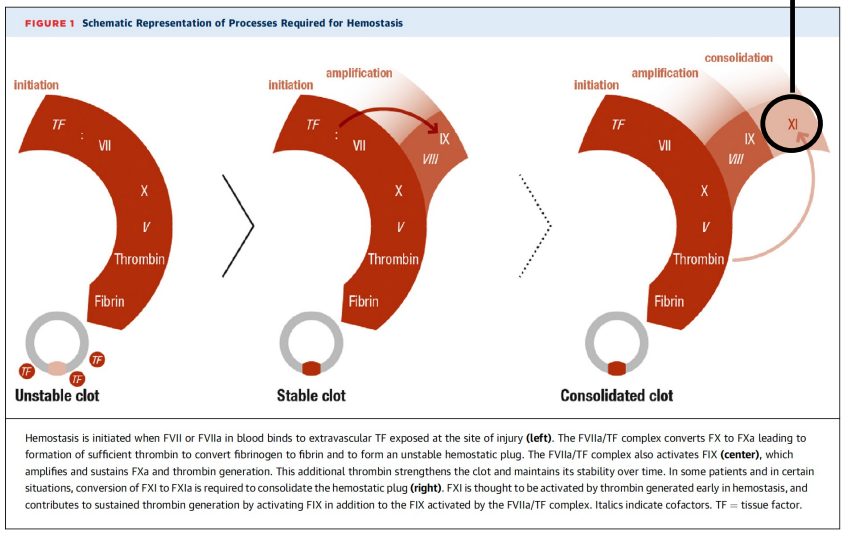



**FIGURE 1** Schematic Representation of Processes Required for Hemostasis

Hemostasis is initiated when FVII or FVIIa in blood binds to extravascular TF exposed at the site of injury **(left)**. The FVIIa/TF complex converts FX to FXa leading to formation of sufficient thrombin to convert fibrinogen to fibrin and to form an unstable hemostatic plug. The FVIIa/TF complex also activates FIX **(center)**, which amplifies and sustains FXa and thrombin generation. This additional thrombin strengthens the clot and maintains its stability over time. In some patients and in certain situations, conversion of FXI to FXIa is required to consolidate the hemostatic plug **(right)**. FXI is thought to be activated by thrombin generated early in hemostasis, and contributes to sustained thrombin generation by activating FIX in addition to the FIX activated by the FVIIa/TF complex. Italics indicate cofactors. TF = tissue factor.

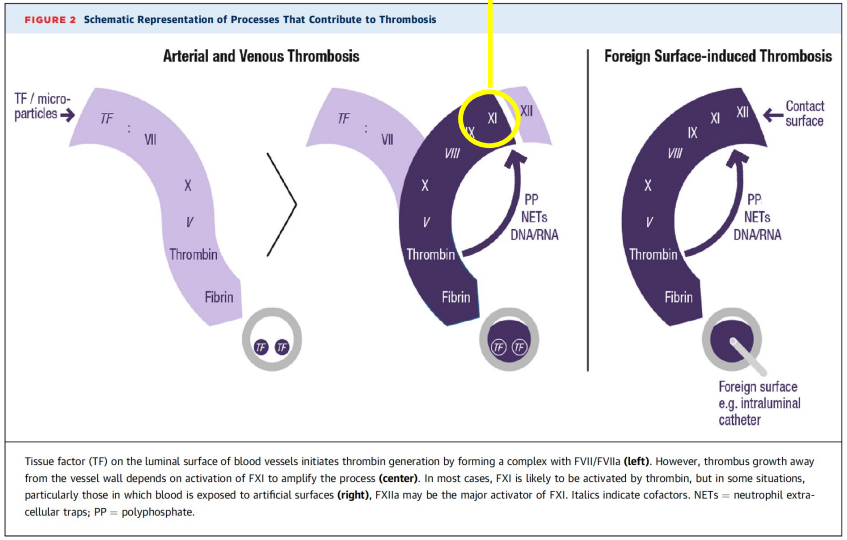



**FIGURE 2** Schematic Representation of Processes That Contribute to Thrombosis

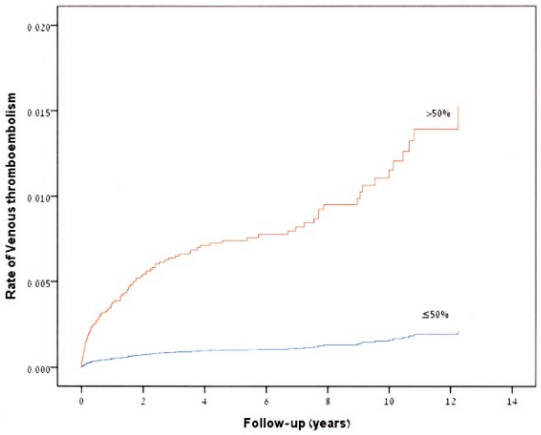
Tissue factor (TF) on the luminal surface of blood vessels initiates thrombin generation by forming a complex with FVII/FVIIa **(left)**. However, thrombus growth away from the vessel wall depends on activation of FXI to amplify the process **(center)**. In most cases, FXI is likely to be activated by thrombin, but in some situations, particularly those in which blood is exposed to artificial surfaces **(right)**, FXIIa may be the major activator of FXI. Italics indicate cofactors. NETs = neutrophil extracellular traps; PP = polyphosphate.

HSU et Al. JACC VOL . 78, NO. 6, 2021

# Pour le futur

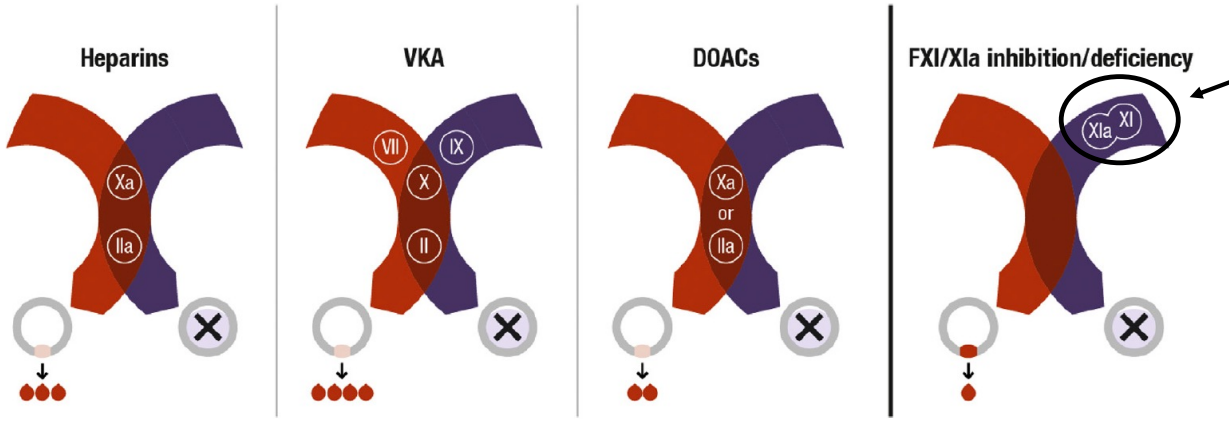
- Nouvelles cibles pour l'anticoagulation
  - Inhibition du **Fx XI**

| | Fx XI | n | Événements | HR ajusté |
|---|---|---|---|---|
| **Événement cardiovasculaire** | ≤30 %<br>30-50 %<br>>50 % | 542<br>693<br>8958 | 19<br>16<br>230 | 0.57 (0.35-0.93)<br>0.52 (0.31-0.87)<br>Référence |
| **TEV** | ≤50 %<br>>50 % | 1235<br>8958 | 3<br>94 | 0.26 (0.08-0.84)<br>Référence |




Prins M. et Al, Blood (2017) 129(9):1210-1215.

**FIGURE 3** Impact of Various Anticoagulants on Hemostasis Versus Thrombosis




Current anticoagulants inhibit either FXa or thrombin (IIa) (DOACs), or both (heparins), or reduce synthesis of their precursors (VKAs). This will attenuate thrombosis but also compromise hemostasis. The greater role of FXI in thrombosis relative to hemostasis provides a potential target for hemostasis-sparing anticoagulation. Cross-sectional view of vessels shown with hemostasis in **red** and thrombosis in **purple**. DOACs = direct oral anticoagulants; VKA = vitamin K antagonist.

# Anti-XI

- **Oligonucléotide qui bloque la synthèse hépatique du Fx XI (antisense oligonucleotide)**
  - **FXI-ASO[1]**
  - S/C et débuté 36 jours avant la chirurgie puis 3 jours post-op
- **Anticorps monoclonaux**
  - **Abelacimab[2]**
  - 1 dose IV (de 4h à 8h post-op)
  - **Osocimab[3]**
  - 1 dose IV (pré ou post-op)
- **Inhibiteur oral du fx XIa**
  - **Milvexian[4]**
  - Absorption rapide, demi-vie 12h

*1) Buller HR. et Al. N Engl J Med 2015;372:232-40.*
*2) Verhamme P. et Al. N Engl J Med 2021;385:609-17.*
*3) Weitz J. et Al. JAMA. 2020;323(2):130-139.*
*4) Weitz J. et Al. N Engl J Med 2021;385:2161-72.*

# Études de phase II en PTG

ORIGINAL ARTICLE

## Abelacimab for Prevention of Venous Thromboembolism

Peter Verhamme, M.D., B. Alexander Yi, M.D., Ph.D., Annelise Segers, M.D., Janeen Salter, B.S.N., Daniel Bloomfield, M.D., Harry R. Büller, M.D., Gary E. Raskob, Ph.D., and Jeffrey I. Weitz, M.D., for the ANT-005 TKA Investigators*

ORIGINAL ARTICLE

## Factor XI Antisense Oligonucleotide for Prevention of Venous Thrombosis

Harry R. Büller, M.D., Claudette Bethune, Ph.D., Sanjay Bhanot, M.D., Ph.D., David Gailani, M.D., Brett P. Monia, Ph.D., Gary E. Raskob, Ph.D., Annelise Segers, M.D., Peter Verhamme, M.D., and Jeffrey I. Weitz, M.D., for the FXI-ASO TKA Investigators*

ORIGINAL ARTICLE

## Milvexian for the Prevention of Venous Thromboembolism

Jeffrey I. Weitz, M.D., John Strony, M.D., Walter Ageno, M.D., David Gailani, M.D., Elaine M. Hylek, M.D., Michael R. Lassen, M.D., Kenneth W. Mahaffey, M.D., Ravi S. Notani, M.B.A., Robin Roberts, M.S., Annelise Segers, M.D., and Gary E. Raskob, Ph.D., for the AXIOMATIC-TKR Investigators*

JAMA | Original Investigation

## Effect of Osocimab in Preventing Venous Thromboembolism Among Patients Undergoing Knee Arthroplasty

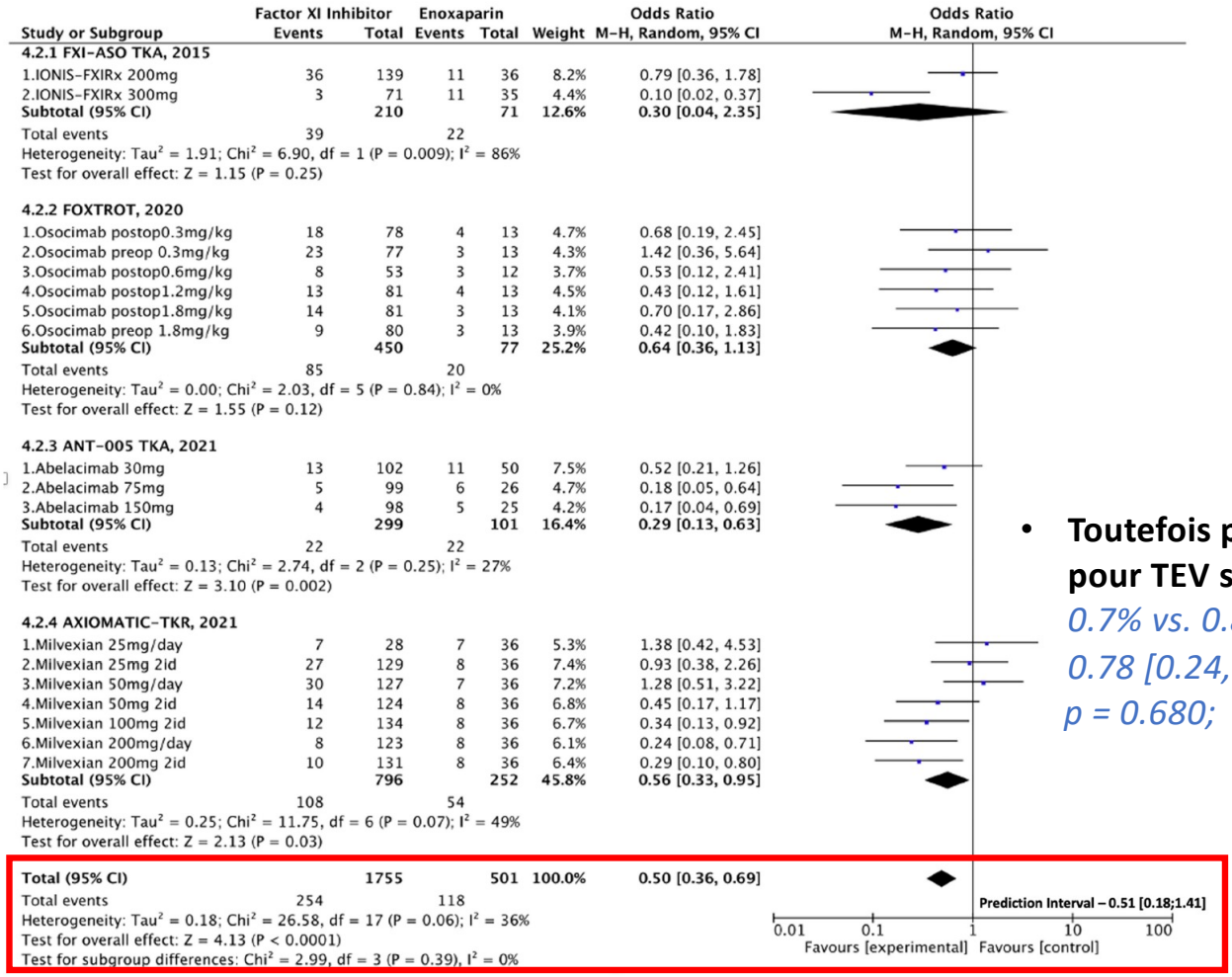
### The FOXTROT Randomized Clinical Trial

Jeffrey I. Weitz, MD; Rupert Bauersachs, MD; Bastian Becker, MSc; Scott D. Berkowitz, MD; Maria C. S. Freitas, MD, PhD; Michael R. Lassen, MD; Carola Metzig, MD; Gary E. Raskob, PhD

TABLE 1 Characteristics of each study and study medication

| *Characteristics* | FXI-ASO TKA, 2015[9] | FOXTROT, 2020[10] | ANT-005 TKA, 2021[11] | AXIOMATIC-TKR, 2021[12] |
|---|---|---|---|---|
| Study medication–n | FXI-ASO–221 patients | Osocimab–450 patients | Abelacimab–299 patients | Milvexian–796 patients |
| Type of agent | Second generation antisense oligonucleotide | Monoclonal antibody (fully human) | Monoclonal antibody (fully human) | Small molecule |
| Mode of action | Decreases FXI synthesis | FXia inhibition | Dual FXI/XIa inhibition | FXia inhibition |
| Administration route | Subcutaneous | Intravenous | Intravenous | Oral |
| Dose | 200/300 mg | 0.3/0.6/1.2/1.8 mg/kg | 30/75/150 mg | 25/50/100/200 mg |
| Administration frequency | First administration was 36 days before surgery (day 1); then on days 3, 5, 8, 15, 22, 29, 36 (6 h after surgery), and 39. | Single administration the day before/ after surgery | Single administration 4–8 h after surgery | Once/twice a day for 10 to 14 days–first dose 12/24 h after surgery |
| Comparator–n | Enoxaparin 40 mg s.c.–72 patients-first dose in the evening before or 6 h post-op | Enoxaparin 40 mg s.c.–77 patients-first dose in the evening before or 6-8 h post-op | Enoxaparin 40 mg s.c.–101 patients-first dose in the evening before or 12 h post-op | Enoxaparin 40 mg s.c.–252 patients-first dose the day before surgery |
| Duration of comparator treatment–median | 10 days [10; 10] | 13 days [10; 16] | 9 days [6; 12] | 12 days [1; 15] |
| Trial design | Randomized, parallel-group, adaptive design, open-label with blinded outcome adjudication | Randomized, parallel-group, adaptive design, open-label with blinded outcome adjudication | Randomized, parallel-group, open-label with blinded outcome adjudication | Randomized, parallel-group, adaptive design, open-label with blinded outcome adjudication |
| Age | 63–64 years | 66.5 ± 8.2 years | 67–68 years | 68–69 years |
| Female–% | 81.2% | 74.2% | 81.8% | 69.4% |
| Venogram timing—days after surgery | 8–12 | 10–13 | 8–12 | 10–14 |
| Time analysis for safety outcomes | 136 days | 150 days | 30 days | On-treatment period +2 days |
| Total VTE events—*n* (%) | 61 (21.7%) | 105 (19.9%) | 44 (11.0%) | 162 (15.5%) |
| *Study medication* | 39 (18.6%) | 85 (18.9%) | 22 (7.4%) | 108 (13.6%) |
| *Enoxaparin* | 31.0%) | 20 (26.0%) | 22 (21.8%) | 54 (21.4%) |
| Total major or clinically relevant non-major bleeding events—*n* (%) | 12 (4.1%) | 22 (3.2%) | 4 (1.0%) | 12 (1.0%) |
| *Study medication* | 6 (2.7%) | 15 (2.6%) | 4 (1.3%) | 7 (0.8%) |
| *Enoxaparin* | 6 (8.3%) | 7 (6.9%) | 0 (0%) | 5 (1.7%) |

Abbreviations: FXI, factor XI; VTE, venous thromboembolism.




- **Toutefois pas de différence pour TEV symptomatiques** :
  *0.7% vs. 0.8%, OR [95% CI] = 0.78 [0.24, 2.57];*
  *p = 0.680;*

FIGURE 3 Forest plot comparing factor XI inhibitors versus low molecular weight heparin regarding the incidence of venous thromboembolism

Presume J. et Al, *J Thromb Haemost. 2022;00:1–9.*

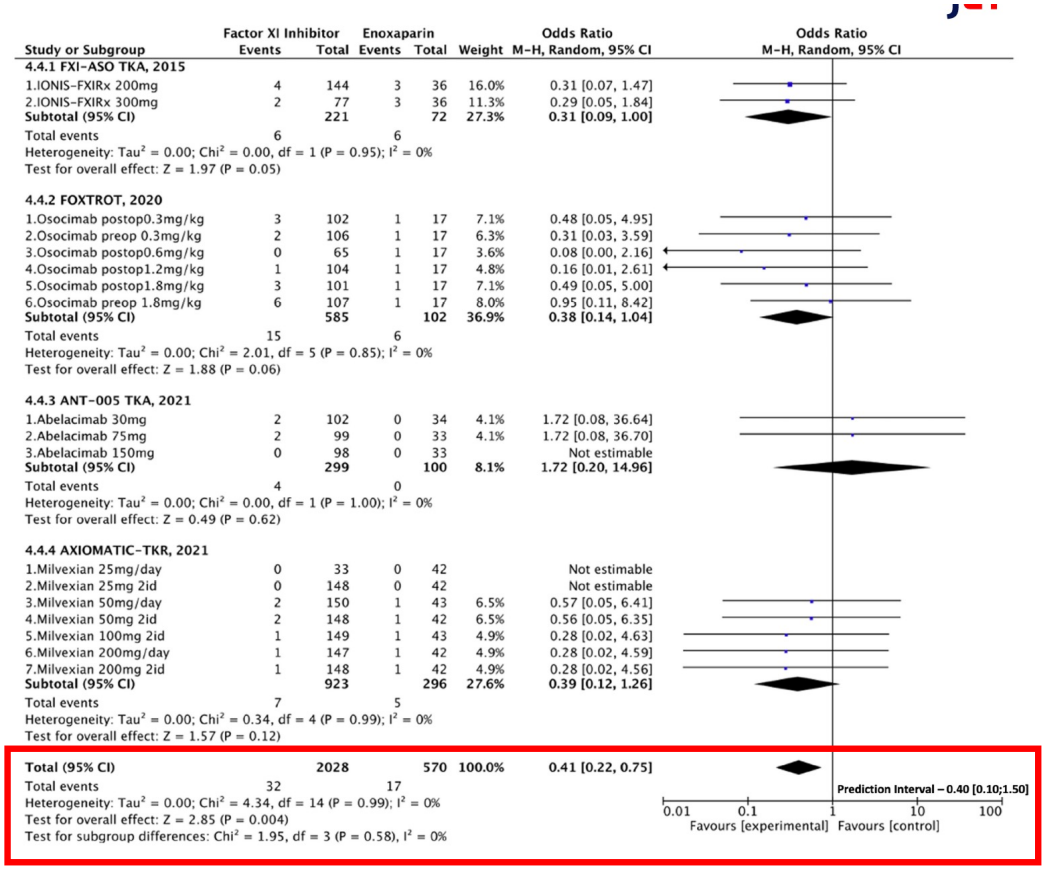



FIGURE 4 Forest plot comparing factor XI inhibitors versus low molecular weight heparin regarding the incidence of major or clinically relevant non-major bleeding events

# Utilisation des dosages supérieurs à HBPM

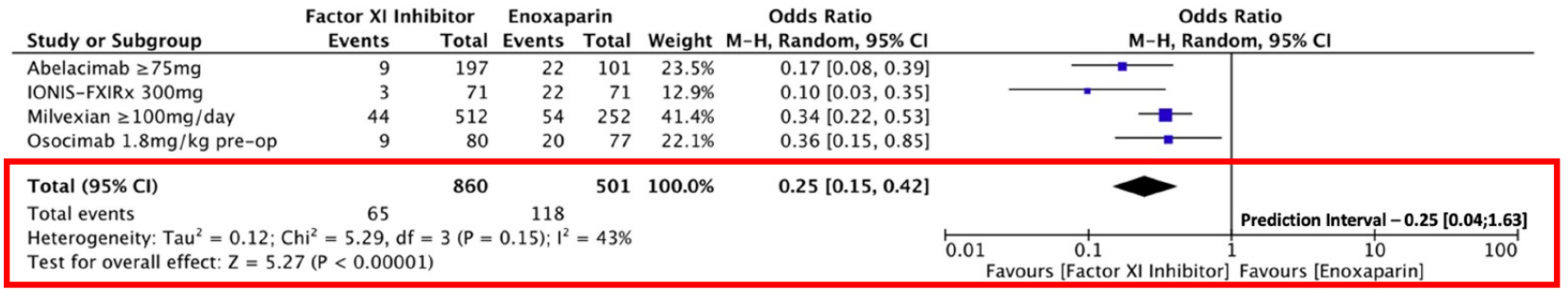



FIGURE 5 Forest plot for the sensitivity analysis comparing factor XI inhibitors dosages that showed superior efficacy to low molecular weight heparin regarding the incidence of venous thromboembolism

Presume J. et Al, *J Thromb Haemost. 2022;00:1–9.*

# Utilisation des dosages supérieurs à HBPM

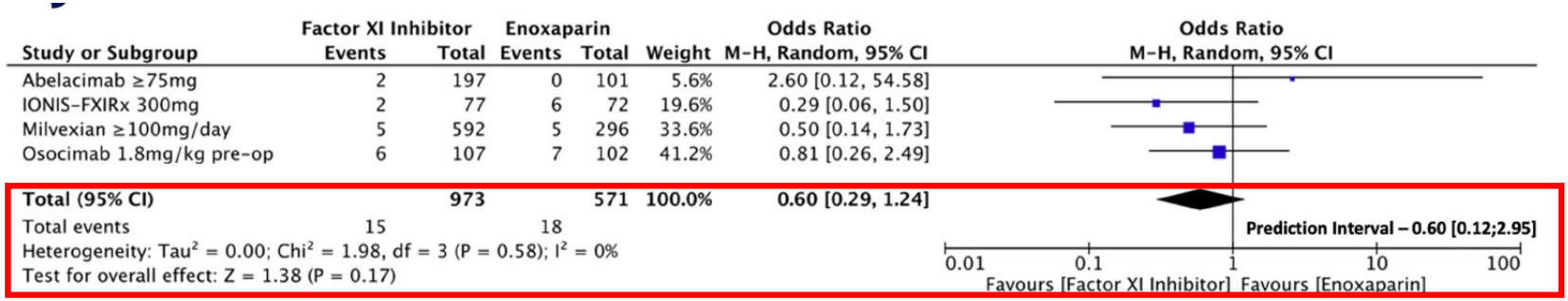



FIGURE 6 Forest plot for the sensitivity analysis comparing factor XI inhibitors dosages that showed superior efficacy to low molecular weight heparin regarding the incidence of major or clinically relevant non-major bleeding events

Presume J. et Al, *J Thromb Haemost. 2022;00:1–9.*

# Conclusion

- Les AOD sont maintenant préférés aux HBPM
- Chez les patients à bas risque une stratégie hybride Rivaroxaban et ASA est sécuritaire (EPCAT II)
- Le rôle de l'ASA seule reste à préciser (EPCAT III à venir)
- L'inhibition du Fx XI est la cible d'avenir en thromboprophylaxie orthopédique

Merci !

Questions ?