Perioperative thromboprophylaxis and management of antithrombotic therapy: an update

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RÉUNION SORBCOT – 19.03.22 -

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Highlights

- Thromboprophylaxis in major orthopedic surgery
  - Balancing venous thromboembolism (VTE) and bleeding risks
  - Concept of population versus individual approach
  - Role of aspirin
  - Practical approach
- Thromboprophylaxis after knee arthroscopy or distal leg injury
- Perioperative management of anticoagulated patients
  - Assessing risk for thrombotic and risk for perioperative bleeding
  - Benefits and harms of bridging anticoagulation
  - Overall periprocedural antithrombotic strategy

Thrombophophylaxis after major arthroplasty (THA/TKA)

Many guidelines - little consensus ?

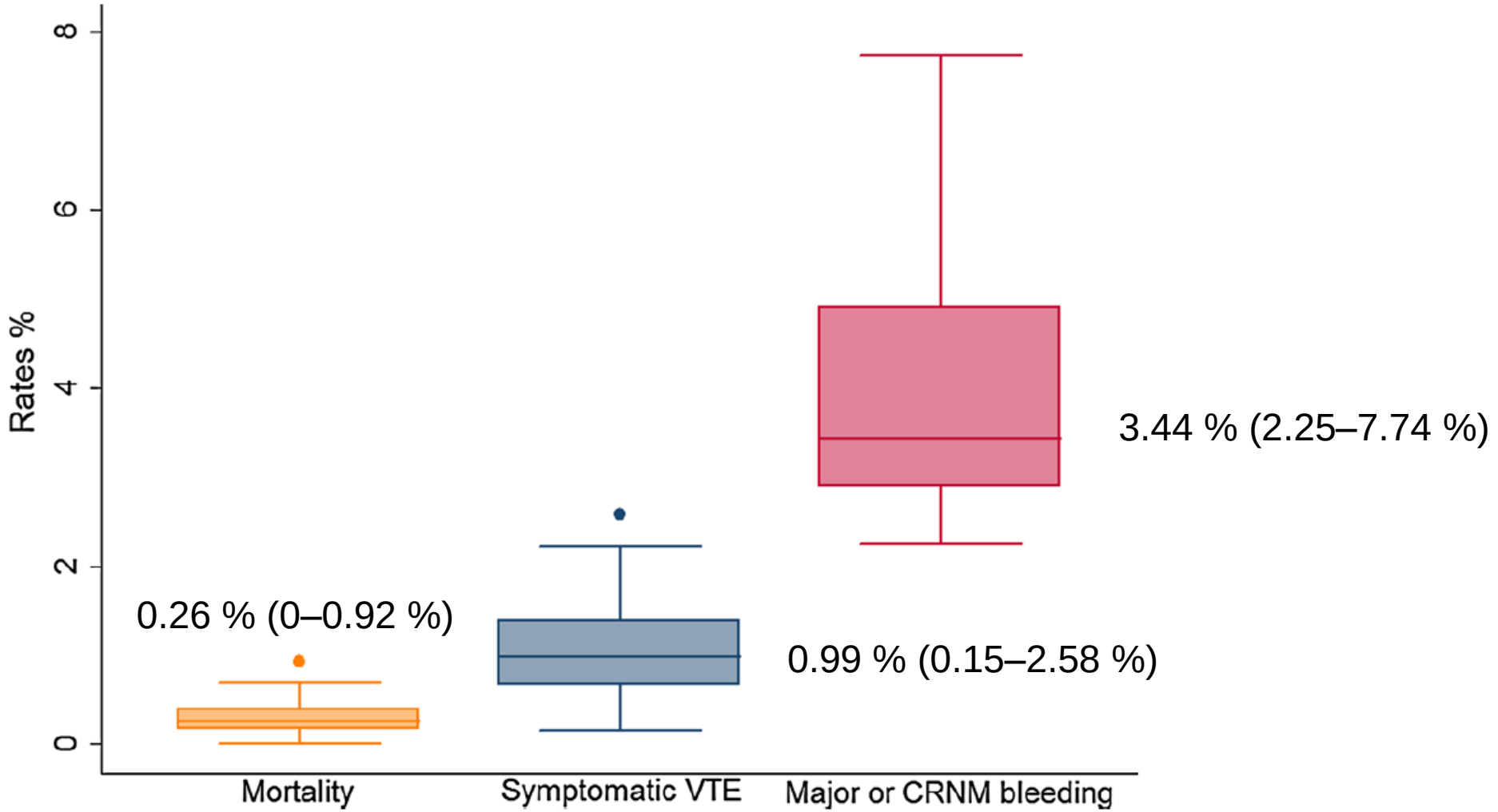
	Choice of prophylaxis regimen
ACCP 2012	• LMWH, fondaparinux, apixaban, dabigatran, rivaroxaban, low-dose unfractionated Heparin, adjusted-dose vitamin K antagonist, aspirin (all Grade 1B) , or IPCD (Grade 1C) • LMWH (in preference, Grade 2C) • For a minimum of 10 to 14 days, extended thromboprophylaxis after THA for up to 35 days
AAOS 2012	• No recommendations regarding the use of a specific prophylaxis regimen
NICE 2018	• THA: LMWH for 10 days followed by aspirin (75 or 150 mg) for a further 28 days or LMWH for 28 days combined with anti-embolism stockings, or rivaroxaban or apixaban or dabigatran • TKA: Aspirin or LMWH for 14 days, or rivaroxaban or apixaban or dabigatran
ESA 2018	• Aspirin in patients without a high VTE risk, for a minimum of 7 days (Grade 1B)
ASH 2019	• Aspirin or anticoagulants (⊕◯◯◯) • When anticoagulants are used, the panel suggests using DOACs over LMWH

Chest 2012; 141(2)(Suppl):e278S–e325S
J Bone Joint Surg Am. 2012;94:746-7
NICE 2018. www.**nice**.org.uk/guidance/NG89
Eur J Anaesthesiol 2018; 35:134-138
Blood Adv. 2019;3:3898-3944

Thrombophrophylaxis after major orthopedic surgery: balancing VTE and bleeding risks

Systematic review of contemporary randomized trials

Combined patient important event rates for new anticoagulants and enoxaparin, median rate (range)



Chan NC, et al. J Thromb Thrombolysis. 2015;40:231–9

Trends over time toward decreasing rates of VTE after primary total hip replacement

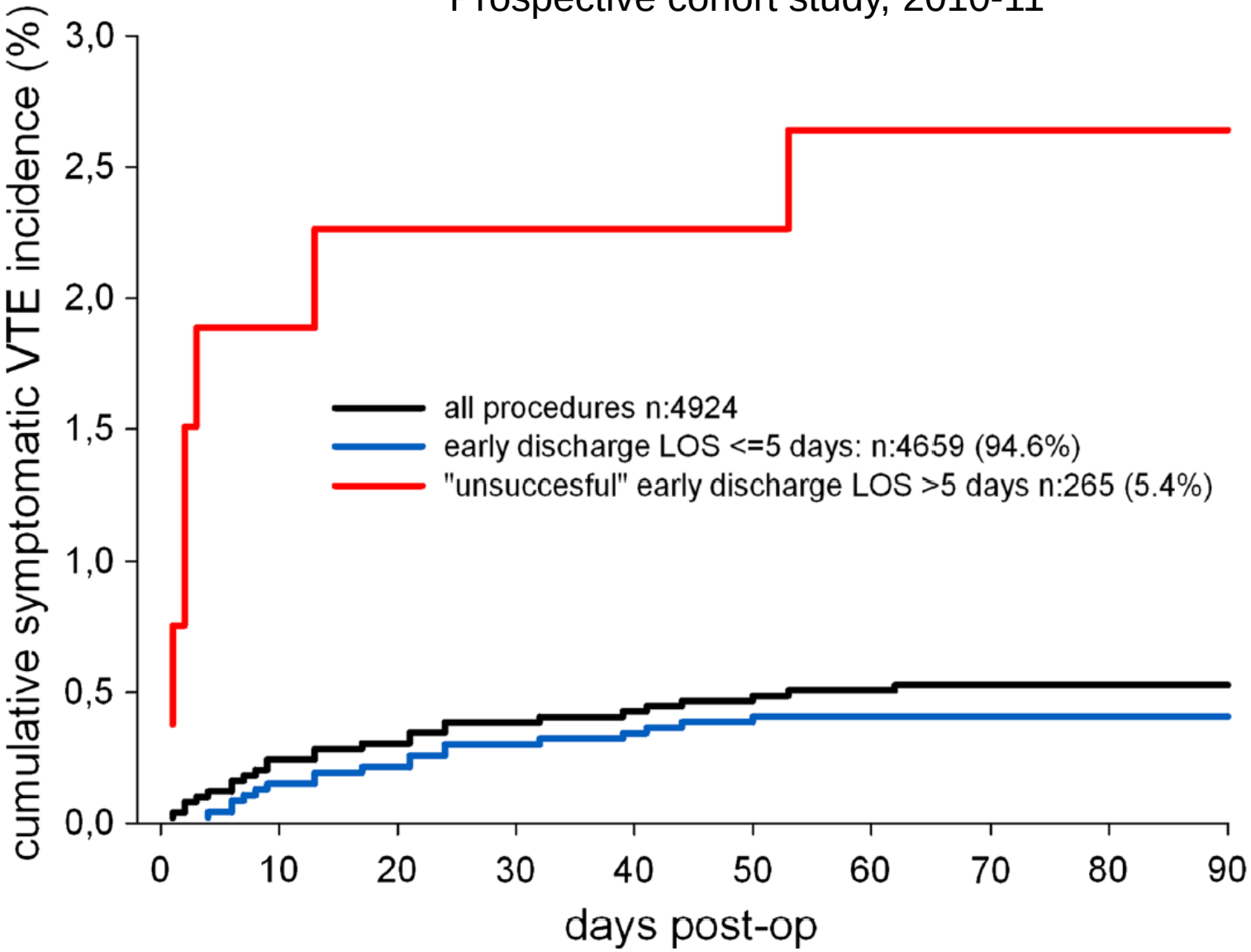
Retrospective cohort study (NHS)

	2005, N = 34,643		2014, N = 40,758	
		90-Day Mortality		90-Day Mortality
Pulmonary embolism, No. (%)	268 (0.77)	18 (6.7)	162 (0.40)	2 (1.23)

Partridge T, et al. J Bone Joint Surg Am. 2018;100:360-7

Low rates of VTE after fast-track THA and TKA with thromboprophylaxis only during hospitalisation in patients with LOS ≤5 days

Prospective cohort study, 2010-11



2.65 % (1.35% to 5.14%)

0.41% (0.26% to 0.64%)

Jorgensen CC, et al. BMJ Open 2013; 3: e003965.

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Concept of individual approach to thromboproprophylaxis

- Individual approach: differentiated prophylaxis based on individual risk assessment including timing of mobilization
- The patient-specific risk factors for VTE may outweigh the contribution of the surgery-specific risk

Individual approach to prophylaxis

- Taking into account patient risk factors for VTE and bleeding in addition to the surgery itself

Main patient risk factors for VTE after major orthopaedic surgery

- Previous VTE
- Hypercoagulable states
- Age > 70
- BMI ≥ 30 kg/m2
- Active cancer
- Medical comorbidities (heart disease, lung disease)
- Neurological deficit
- Severe renal insufficiency

- No risk assessment model (RAM) specific to patients undergoing orthopedic surgery has been validated

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Role of aspirin ?

- Differentiated prophylaxis based on individual risk assessment:
  - Aspirin or
  - Anticoagulant or
  - Sequential prophylaxis including anticoagulant and aspirin

Aspirin compared to anticoagulants for patients undergoing total hip or knee arthroplasty

Meta-analysis of 7 RCT (No: 1884 patients)

	Aspirin, No. (%)	Anticoagulants, No. (%)	RR	Certainty
Symptomatic PE	4/759 (0.5%)	3/1077 (0.3%)	1.49 (0.37- 6.09)	⨁◯◯◯
Symptomatic proximal DVT	8/699 (1.1%)	6/1047 (0.6%)	1.49 (0.51- 4.34)	⨁◯◯◯
Major bleeding	9/505 (1.8%)	2/567 (0.4%)	2.63 (0.64-10.79)	⨁⨁◯◯

Alfaro, M. J. Thromb Haemost. 1986; 56:53-6
Josefsson, G. Acta Orthop Scand 1987;58: 626-9
Lotke, P. A . Clin Orthop Relat Res 1996;324:251-8
Westrich, G. H. J Arthroplasty 2006;21:139-43
Kulshrestha, V. J Arthroplasty. 2013; 28:1868-73
Jiang, Y. Chinese Medical Journal; 2014
Zou, Y. Blood Coagul Fibrinolysis 2014;25:660-4

Anderson DR, et al. Blood Adv. 2019;3:3898-3944

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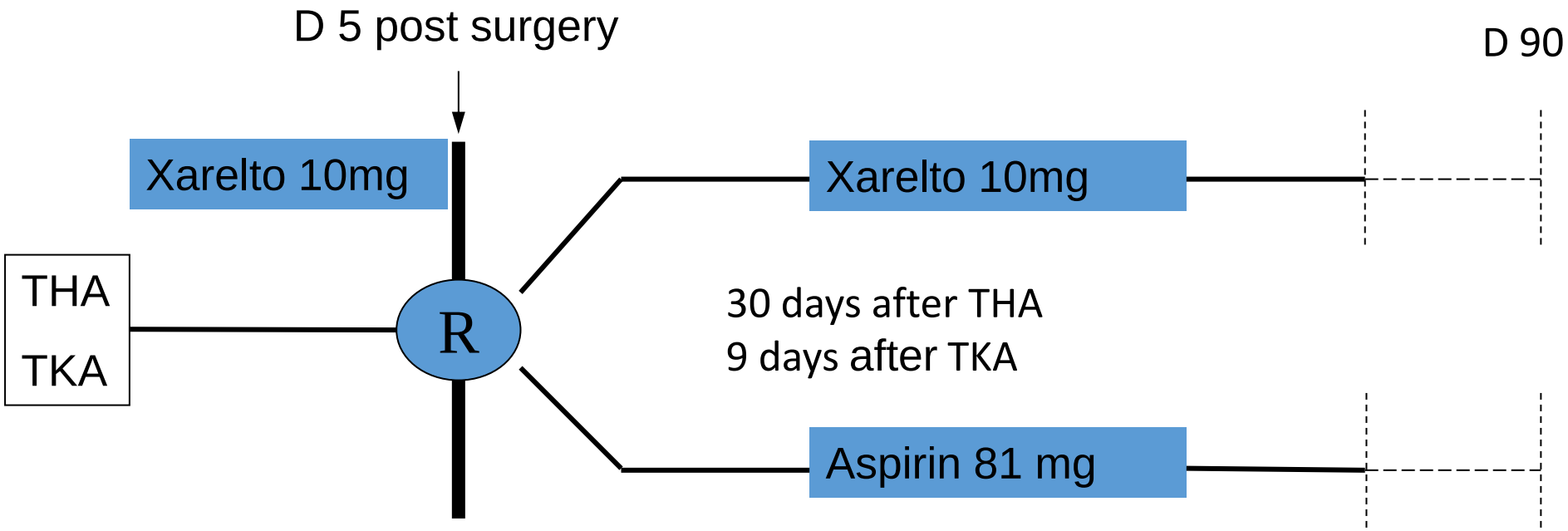
Aspirin or Rivaroxaban for VTE Prophylaxis after Hip or Knee Arthroplasty

Double-blind, randomized, noninferiority trial



Primary effectiveness outcome: symptomatic VTE at D 90

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

Aspirin or rivaroxaban for VTE prophylaxis after hip or knee arthroplasty: EPCAT II trial

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

Aspirin was not significantly different from the direct oral anticoagulant after an initial 5-day postoperative course of rivaroxaban.

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

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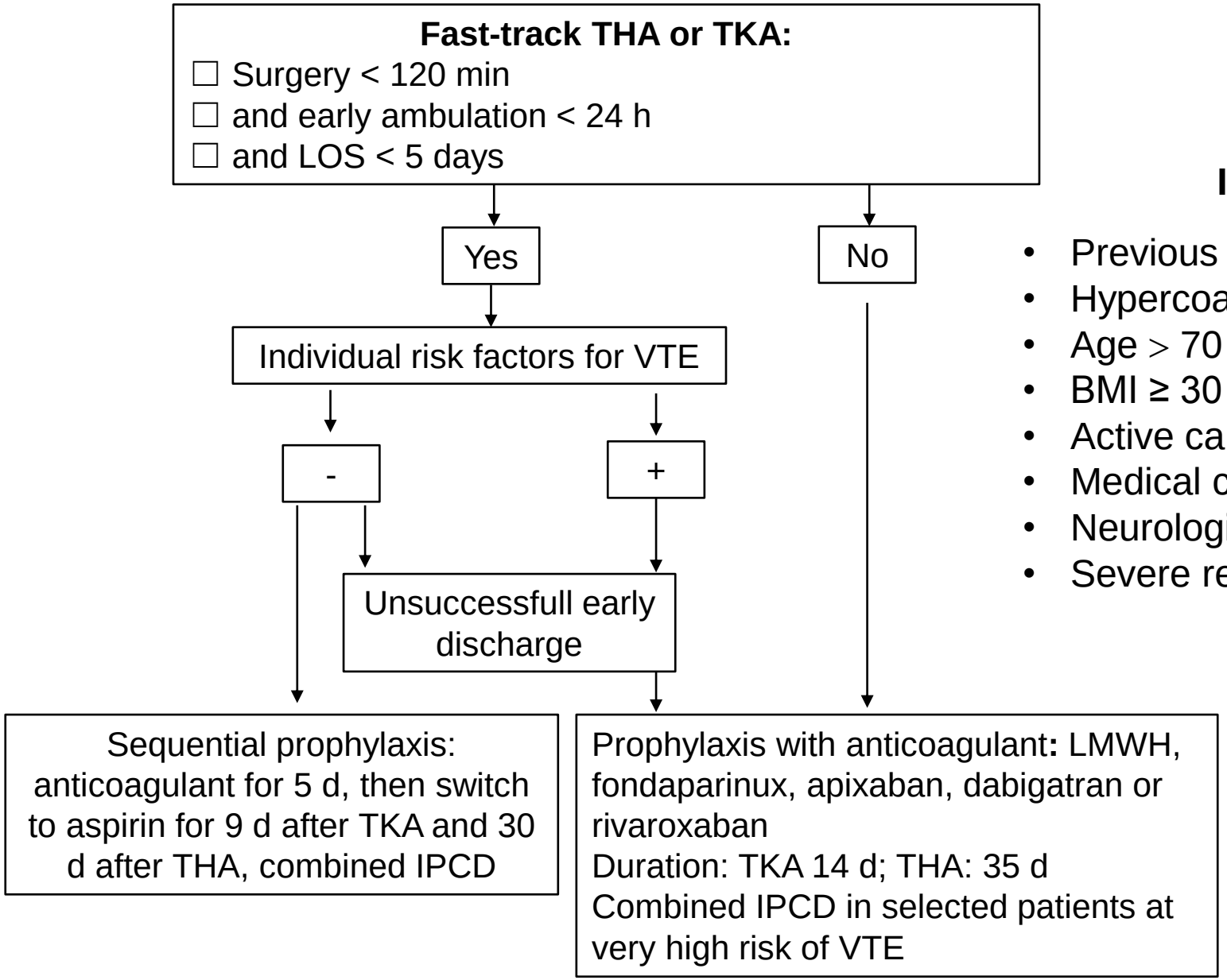
A practical approach



Individual risk factors for VTE

- Previous VTE
- Hypercoagulable states
- Age > 70
- BMI ≥ 30 kg/m2
- Active cancer
- Medical comorbidities (heart disease, lung disease)
- Neurological deficit
- Severe renal insufficiency

Adapted from the recommendations of the GIHP, 2019

What do we need ?

- To validate a risk stratification system to distinguish between low-risk and higher-risk patients
- To definitely establish the place of aspirin in de-escalation randomized trial:
  - Non inferiority regarding efficacy
  - Superiority regarding safety

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Non-major orthopaedic setting

Patients with isolated lower leg injuries distal to the knee

Patients undergoing knee arthroscopy

- The use of prophylaxis remains controversial:
  - Few data are available regarding the benefit-risk ratio of prophylaxis
  - Recommendations vary from one country to another
  - The level of risk often differs according to the type of trauma or surgical procedure

POT-KAST Trial

Multicenter, randomized, controlled, open-label trials in patients undergoing knee arthroscopy

LMWH* :

≤ 100 kg: nadroparin 2850 IU or dalteparin 2500 IU

> 100 kg: double dose in one daily injection

Primary outcome:

symptomatic VTE within 3 months

	Treatment Group (N = 731)*		Control Group (N = 720)		
	n. patients	% (95% CI)	n. patients	% (95% CI)	Relative Risk (95% CI)
Primary outcome	5	0.7 (0.2 to 1.6)	3	0.4 (0.1 to 1.2)	1.6 (0.4 to 6.8)
DVT	4	0.5 (0.1 to 1.4)	2	0.3 (0 to 1.0)	
Pulmonary embolism	1	0.1 (0 to 0.8)	1	0.1(0 to 0.8)	
DVT and pulmonary embolism	0	0 (0 to 0.5)	0	0 (0 to 0.5)	

van Adrichem RA, et. N Engl J Med 2017;376:515-25

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LMWH* :

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> 100 kg: double dose in one daily injection

Primary outcome:
symptomatic VTE within 3 months

	Treatment Group (N = 719)*		Control Group (N = 716)		
	n. patients	% (95% CI)	n. patients	% (95% CI)	Relative Risk (95% CI)
Primary outcome	10	1.4 (0.7 to 2.5)	13	1.8 (1.0 to 3.1)	0.8 (0.3 to 1.7)
DVT	6	0.8 (0.3 to 1.8)	8	1.1 (0.5 to 2.2)	
Pulmonary embolism	3	0.4 (0.1 to 1.2)	4	0.6 (0.2 to 1.4)	
DVT and pulmonary embolism	1	0.1 (0 to 0.8)	1	0.1 (0 to 0.8)	

van Adrichem RA, et. N Engl J Med 2017;376:515-25

Non-major orthopaedic setting
Towards an individualised approach to VTE prevention

- Identifying:
  - Low-risk patients who can be safely withheld from treatment
  - High-risk patients who could be treated possibly with a higher dose or longer duration of therapy
- Validation by large management studies is needed

Risk assessment model for VTE in lower-leg cast patients

TRiP(cast) score.[a]

	Points
Trauma[b]	
High-risk trauma	**3**
Fibula and/or tibia shaft fracture	
Tibial plateau fracture	
Achilles tendon rupture	
Intermediate-risk trauma	**2**
Bi or tri-malleolar ankle fracture	
Patellar fracture	
Ankle dislocation, Lisfranc injury	
Severe knee sprain (with edema/haemarthrosis)	
Severe ankle sprain (grade 3)	
Low-risk trauma	**1**
Single malleolar ankle fracture	
Patellar dislocation	
(Meta)Tarsal bone(s) or forefoot fracture	
Non-severe knee sprain or ankle sprain (grade 1 or 2)	
Significant muscle injury	
Immobilization[c]	
Upper-leg cast	**3**
Lower-leg cast	**2**
Foot cast (ankle free) or any semi-rigid without plantar support	**1**
Other cast or bracing with plantar support	**0**

TRiP(cast) score.[a]

	Points
Patient characteristics[d]	
Age <35 years	**0**
Age ≥35 and <55 years	**1**
Age ≥55 and <75 years	**2**
Age ≥75 years	**3**
Male sex	**1**
Body Mass Index BMI ≥25 and <35 kg/m^2	**1**
Body Mass Index BMI ≥35 kg/m^2	**2**
Family history of VTE (first-degree relative)	**2**
Personal history of VTE or known major thrombophilia	**4**
Current use of oral contraceptives or Estrogenic hormone therapy	**4**
Cancer diagnosis within the past 5 years	**3**
Pregnancy or puerperium	**3**
Immobilization (other) within the past 3 months[e]	**2**
Hospital admission, bedridden or flight > 6 h, Lower limb paralysis	
Surgery within the past 3 months	**2**
Comorbidity	**1**
Heart failure, rheumatoid arthritis, chronic kidney disease, COPD, IBD	
Chronic venous insufficiency *(varicose veins)*	**1**

Mean absolute risk of symptomatic VTE in the POT-CAST population :
< 7 points: 0.8%
≥ 7 points : 2.5%

B. Nemeth et al. EClinicalMedicine 2020; 20: 100270

Risk assessment model for VTE in knee arthroscopy patients

L-TRiP(ascopy) Score	Points
Age ≥ 35 and < 55	2
Age > 55	3
Male sex	1
Current use of oral contraceptives	3
Family history of VTE (1 family member)	2
Family history of VTE (2 family members)	3
Bedridden within the past 3 months	3
Varicose veins	1
Congestive heart failure	1
Knee arthroscopy	4
Ligament reconstruction	6

Provide thromboprohylaxis si score ≥ 8

Nemeth B, Cannegieter SC. Thromb Res. 2019; 174:62-75

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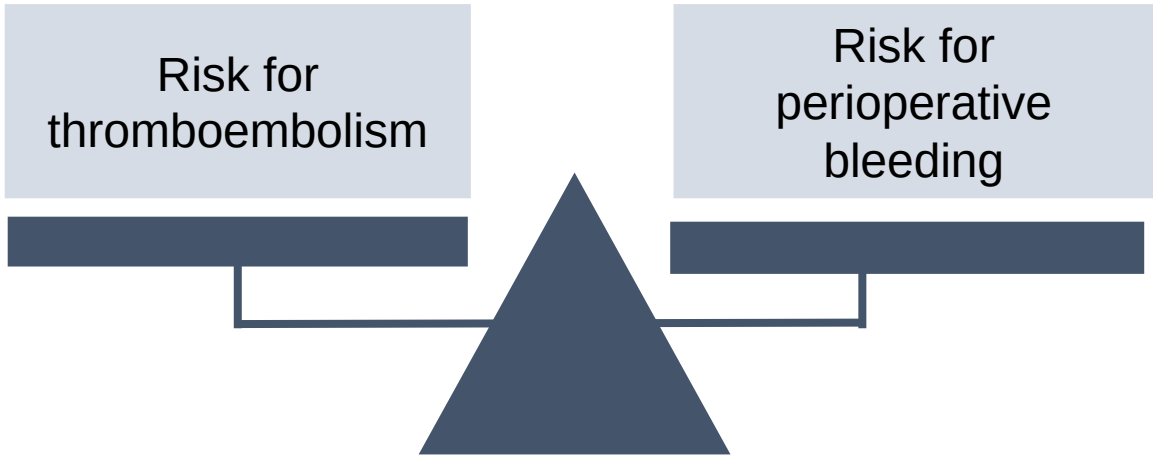
Perioperative management of anticoagulated patients

Assessing risk for thromboembolism and risk for perioperative bleeding

TRADE OFF BETWEEN RISKS



High periprocedural thromboembolic risk patients

- Mechanical heart valve patients other than those with a bileaflet aortic valve and no other risk factors
- AF patients
  - with a previous stroke/TIA in last 3 months **or**
  - with a previous stroke/TIA **and** ≥ 3 risk factors:
    - congestive cardiac failure,
    - hypertension (>140/90 mmHg or on medication),
    - age >75 years,
    - diabetes mellitus
- Patients with a VTE within previous 3 months **or** very high risk patients (previous VTE whilst on therapeutic anticoagulation, severe thrombophilia)

Adapted from Keeling D et al. Br J Haematol. 2016;175:602-613

Classification of elective surgical interventions according to bleeding risk

Low-risk interventions (i.e. infrequent bleeding or with non-severe clinical impact)

Complex dental procedures

Endoscopy with simple biopsy

Small orthopaedic surgery (foot, hand, arthroscopy, . . .)

High-risk interventions (i.e. frequent bleeding and/or with important clinical impact)

Cardiac surgery

Peripheral arterial revascularization surgery (e.g. aortic aneurysm repair, vascular bypass)

Complex invasive cardiological interventions, including lead extraction, (epicardial) VT ablation, chronic total occlusion PCI etc.

Neurosurgery

Spinal or epidural anaesthesia; lumbar diagnostic puncture

Complex endoscopy (e.g. multiple/large polypectomy, ERCP with sphincterotomy etc.)

Abdominal surgery (incl. liver biopsy)

Thoracic surgery

Major urologic surgery/biopsy (incl. kidney)

Extracorporeal shockwave lithotripsy

Major orthopaedic surgery

Steffel J, et al. Europace 2021; 23: 1612–1676

Overall periprocedural antithrombotic strategy

- Patients on VKAs
  - When to consider bridging with treatment dose heparin ?
- Patients on direct oral anticoagulant (DOAC)

No bridging anticoagulation is noninferior to perioperative bridging with LMWH

The BRIDGE study: 1884 AF patients enrolled

Outcome	No Bridging (N = 918)	Bridging (N = 895)	P Value
	number of patients (percent)		
Primary			
Arterial thromboembolism	4 (0.4)	3 (0.3)	0.01*, 0.73†
Stroke	2 (0.2)	3 (0.3)	
Transient ischemic attack	2 (0.2)	0	
Systemic embolism	0	0	
Major bleeding	12 (1.3)	29 (3.2)	0.005†

* P value for noninferiority; † P value for superiority.

JD Douketis et al. N Engl J Med. 2015;373:823-33

When to consider bridging with treatment dose heparin or LMWH in patients who stop VKA treatment ?

- Mechanical heart valve patients other than those with a bileaflet aortic valve and no other risk factors
- AF patients
  - with a previous stroke/TIA in last 3 months **or**
  - with a previous stroke/TIA **and** ≥ 3 risk factors:
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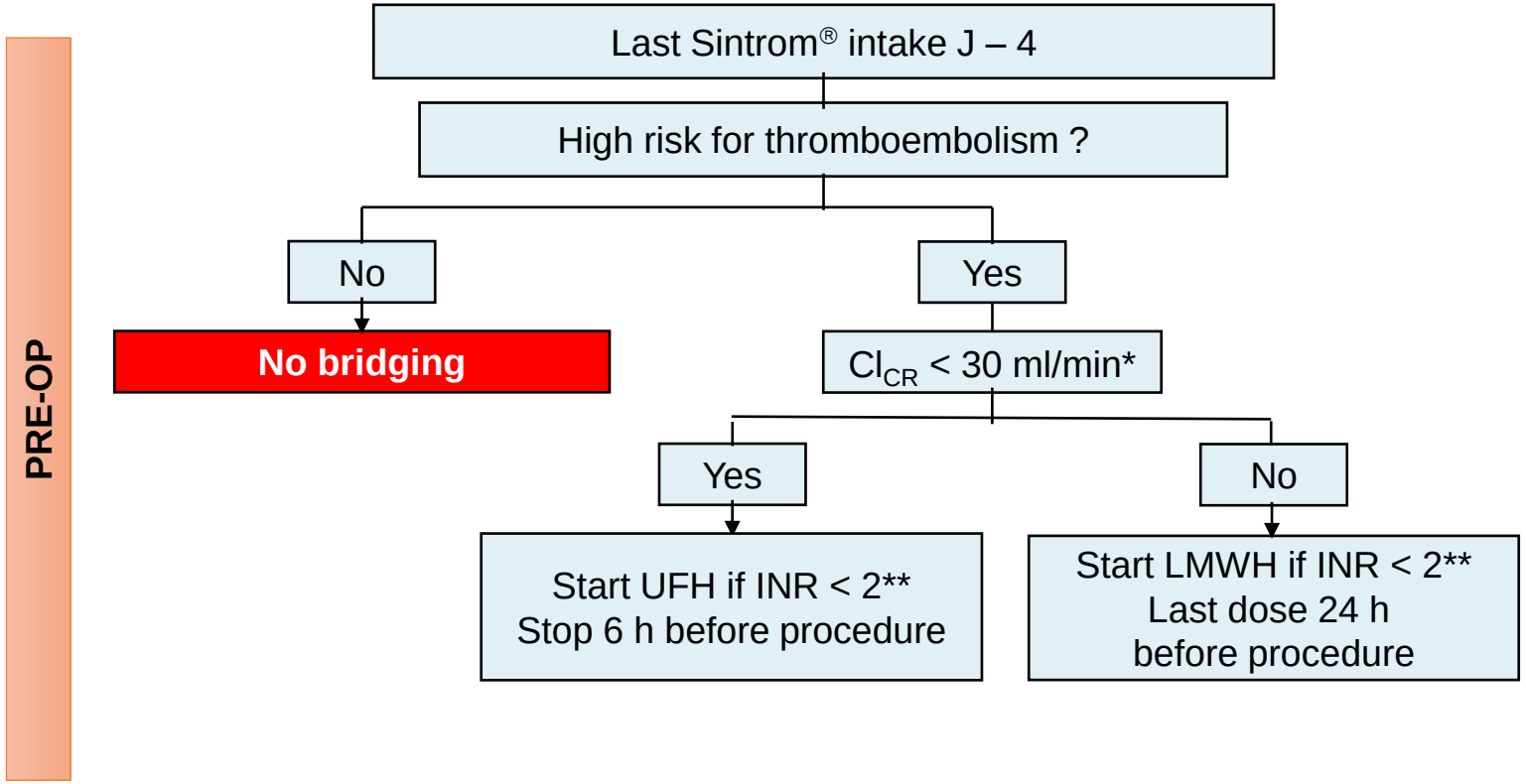
Overall periprocedural antithrombotic strategy

Sintrom®

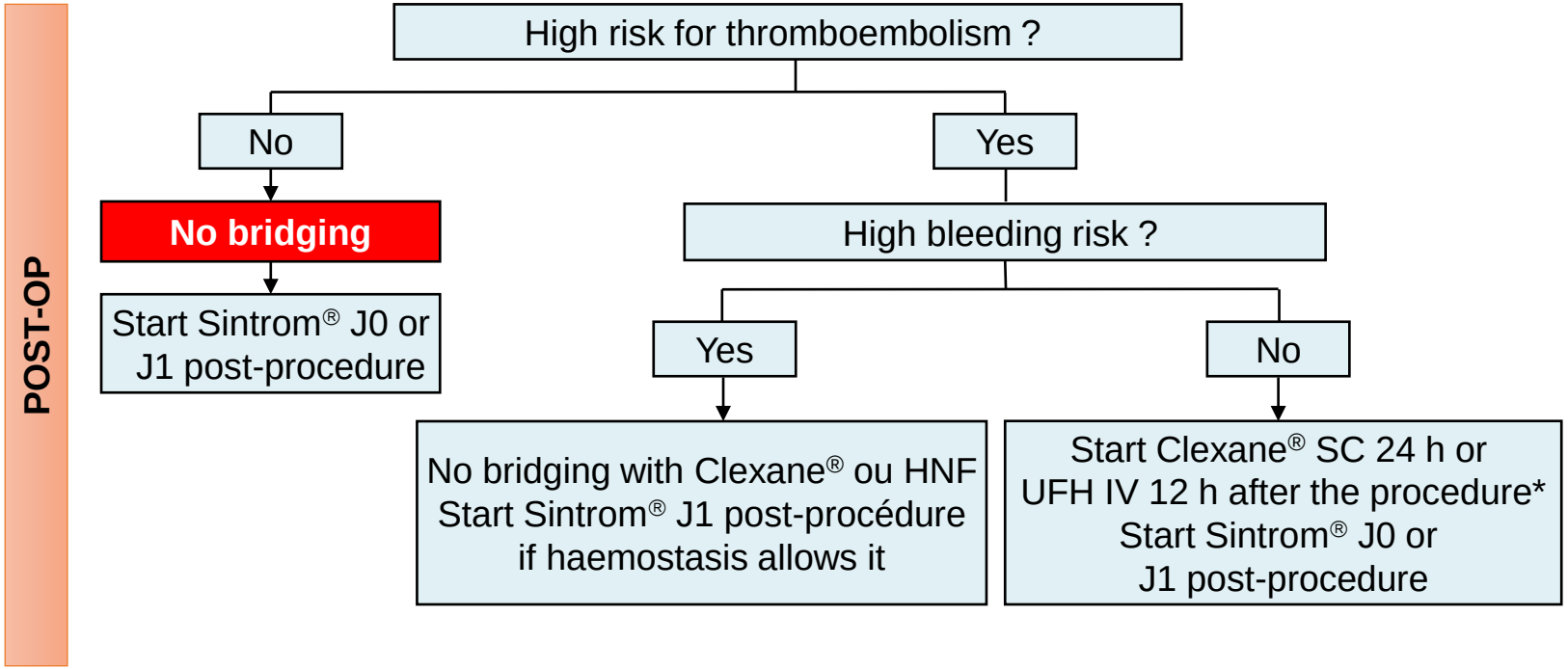


* Cl_{CR} : clairance de la créatinine selon la formule de Cockcroft & Gault

** En pratique, débuter le lendemain de l'arrêt du Sintrom® :
Clexane® 1 mg/kg/12 h; HNF iv : héparine non fractionnée, 15 UI/kg/h (pas de bolus)

Overall periprocedural antithrombotic strategy

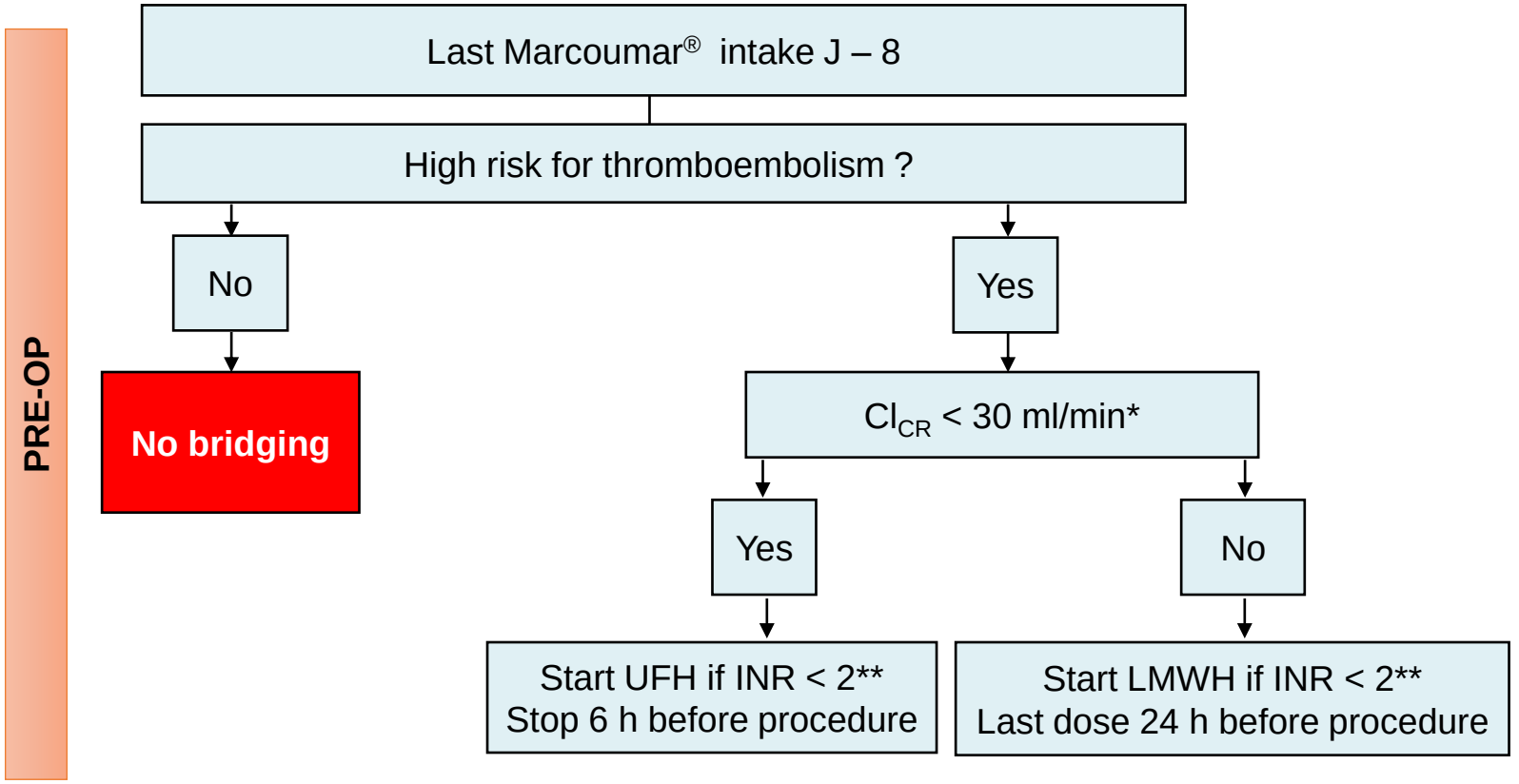
Sintrom®



* Clexane® 1 mg/kg/12 h
HNF iv : héparine non fractionnée, dose d'entretien pré-opératoire (pas de bolus)

Overall periprocedural antithrombotic strategy

Marcoumar®



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Overall periprocedural antithrombotic strategy

Patients on direct oral anticoagulants (DOACs)

Pharmacological characteristics. The essentials

Characteristics	**Dabigatran (Pradaxa®)**	**Rivaroxaban (Xarelto®)**	**Apixaban (Eliquis®)**	**Edoxaban (Lixiana®)**
Tmax (h)	2	2-4	1-4	1-2
Half life	14 à 17 h	7 à 13 h	10 à 14 h	9 à 11h
Renal elimination	80%	35%	27%	50%

Overall periprocedural antithrombotic strategy
Patients on direct oral anticoagulants (DOACs)

- Low bleeding risk interventions:
  - Time of last DOAC dose before: 2 à 3 x half-lives
  - Postoperative resumption 24 h after the procedure
- High bleeding risk interventions:
  - Time of last DOAC dose before: 4-5 half-lives
  - Postoperative resumption delayed for at least 48 h - 72 h
- No bridging unless resumption of oral treatment is delayed

Spyropoulos AC et Douketis JD. Blood 2012;120:2954-62

Timing of last NOAC intake before an elective intervention

	Dabigatran		Apixaban - Edoxaban - Rivaroxaban	
No perioperative bridging with LMWH / UFH				
Minor risk procedures: - Perform procedure at NOAC trough level (i.e., 12 h / 24 h after last intake). - Resume same day or latest next day.				
	Low risk	**High risk**	**Low risk**	**High risk**
CrCl ≥80 ml/min	≥ 24 h	≥ 48 h	≥ 24 h	≥ 48 h
CrCl 50-79 ml/min	**≥ 36 h**	**≥ 72 h**		
CrCl 30-49 ml/min	**≥ 48 h**	**≥ 96 h**		
CrCl 15-29 ml/min	Not indicated	Not indicated	**≥ 36 h**	
CrCl <15 ml/min	No official indication for use			

Important:

- Timing of interruption may require adaptation based on individual patient characteristics (Fig. 13)
- In patients / situations with risk of NOAC accumulation (renal insufficiency, older age, concomitant medication, see Fig. 6) pausing the NOAC 12-24 hours earlier may be considered.[207,208]
- Resume full dose of NOAC 24h after low-risk- and 48 (-72) h after high-risk interventions

Steffel J, et al. Europace 2021; 23: 1612–1676

Conclusions

- Thrombophrophylaxis should be tailored from the assessment of both patient and procedure-related risk factors
- THA or TKA
  - Low-risk patients: anticoagulant for 5 days then aspirin
  - Higher-risk patients: prophylaxis with an anticoagulant, TKA 14 days; THA: 35 days
- Non-major orthopaedic setting
  - Differentiated prophylaxis based on individual risk assessment
    - Low-risk patients who can be withheld from treatment
    - High-risk patients who could be treated possibly with a higher dose of LMWH or DOACs or longer duration of therapy

Conclusions

- In case of temporary discontinuation of VKAs:
  - Perioperative heparin bridging increases the risk of bleeding without reducing the thromboembolic risk
  - Perioperative bridging only if high thromboembolic risk and low bleeding risk procedure
- No bridging in patients on DOAC unless resumption of oral treatment is delayed