Gestion péri-précédurale et permutations AVK-AOD
SSVQ: TVP et FA 9 décembre 2016

- Stratégies selon les risques de saignement vs thrombose
  - Relais pour IRC, néo, thrombophilie et filtres VCI
- Reprise AC post-précédurale et permutations AVK-AOD

Sylvie Desmarais et André Roussin MD, FRCPC
Avec la collaboration de Jim Douketis, MD, FRCPC

Thrombosis Canada
Thrombose Canada

SSVQ
Société des sciences vasculaires du Québec

Andre Roussin MD

Conflits d'intérêts 2016

Aviseur expert ou comités aviseurs:

Bayer, BI, BMS, Leo, Pfizer, Sanofi

Fonds de recherche:

Astra-Zeneca et Bayer

Conférencier:

Bayer, BI, BMS, Leo, Pfizer etSanofi

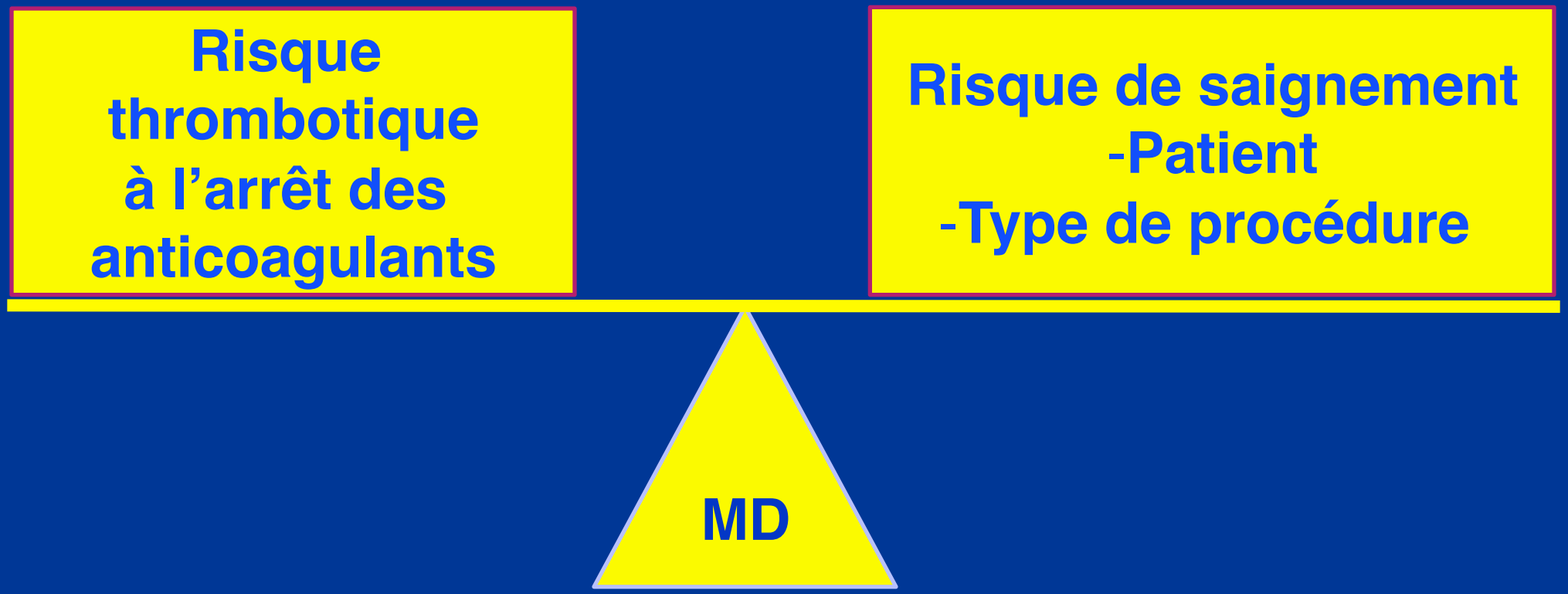
Sylvie Desmarais MD

Conflits d'intérêts 2016

Conférences / Consultante comité aviseurs

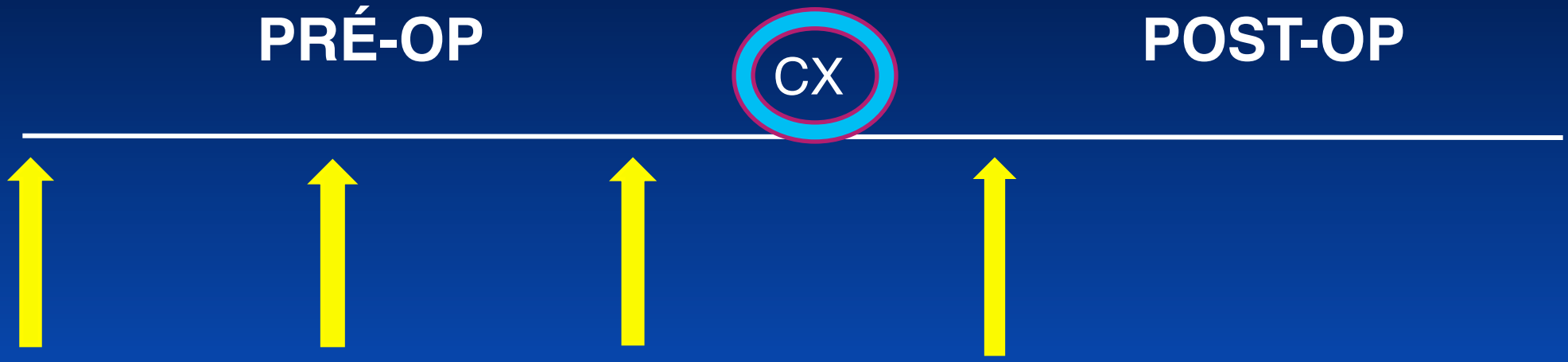
Bayer Health Care, Bristol-Myers Squibb et Pfizer

L'évaluation du risque thrombotique vs hémorragique doit être individualisée



Thérapie de transition avec les AVK

Avant les AOD et l'étude « BRIDGE »



- 5 jours
Arrêt AVK

- 3 jours
HBPM
dose ttx

-1 jour
demi-dose
HBPM

24 à 72 hres selon risque saignement
Reprise HBPM/ HNF ad RIN > 2.0
Reprise AVK

Précédures à risque modéré ou élevé de saignement
AVK, HNF et HBPM

MÉDICAMENT	LABO	GESTION PRÉ-OP	POST-OP
COUMADIN™	RIN	OK si « 1.5 OK si «1.2 si haut risque Arret 5 jrs ou antidote	24-72 hres
Héparine 5000 sc BID ou TID	nil	Arrêt 8-10 hres	2-24 hres
Héparine IV thérapeutique	PTT	OK si « de 1.5 x le témoin Arrêt 4-6 hres	12/24 hres
HBPM dose prophylaxie	nil	Arrêt 12 hres	12/24 hres
HBPM dose thérapeutique	nil	Arrêt 24 hres	12/24 hres (considérer HNF IV)

JVIR 2009/ASRA 2015

A. Roussin MD

Étude BRIDGE

Patients on warfarin who need elective surgery/procedure, interrupt warfarin and randomized to:

(a)bridging (dalteparin 100 IU/kg BID) pre-/post-procedure

(a)no bridging

Douketis JD, Spyropoulos AC, Kaatz S, et al. Perioperative bridging in patients with atrial fibrillation. *N Engl J Med* 2015;373:823

Hypothèses

1) Forgoing bridging anticoagulation would be *non-inferior* to bridging with LMWH for the prevention of perioperative arterial thromboembolism (ATE)

   1% ATE in bridging group, 1% ATE in no bridging group

   - *and* -

2) Forgoing bridging anticoagulation would be *superior* to bridging with respect to major bleeding (MB)

   3% MB in bridging group, 1% MB in no bridging group

Méthodologie

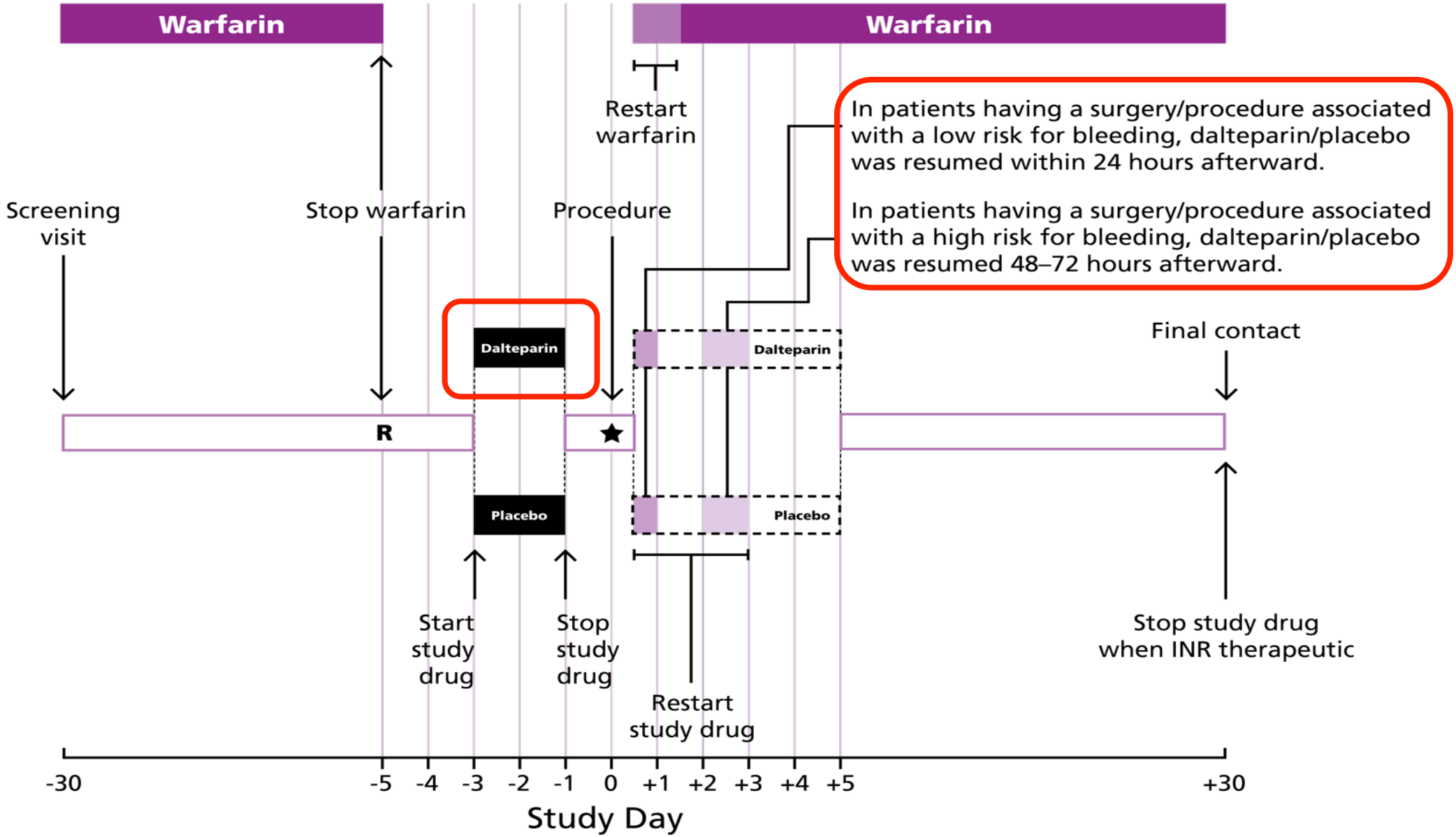
- Randomized, double-blind, placebo-controlled trial
- Patients: AF with $CHADS_2$ ≥1

  (excluded if mechanical heart valve or CrCl <30 mL/min)

- Warfarin stopped 5 days pre-procedure, resumed ≤24 hrs afterwards
- Patients randomized to:
  - bridging with dalteparin, 100 IU/kg BID or matching placebo for 3 days pre- and 5-10 days post-procedure

- Follow-up for 30 days post-procedure

Devis de l'étude BRIDGE



Population étudiée

Characteristic	No Bridging (N=950)	Bridging (N=934)
Age, yr	71.8±8.74	71.6±8.88
Male sex, no. (%)	696 (73.3)	686 (73.4)
Race, no. (%)		
White	860 (90.5)	849 (90.9)
Nonwhite	88 (9.3)	82 (8.8)
Unknown	2 (0.2)	3 (0.3)
Weight, kg	96.2±24.87	95.4±23.50
$CHADS_2$ score		
Mean	2.3±1.03	2.4±1.07
Distribution, no. (%)		
0	1 (0.1)	1 (0.1)
1	216 (22.7)	212 (22.7)
2	382 (40.2)	351 (37.6)
3	229 (24.1)	232 (24.8)
4	96 (10.1)	106 (11.3)
5	23 (2.4)	27 (2.9)
6	3 (0.3)	5 (0.5)

Chirurgies et procédures*

Surgery/Procedure Type	No Bridging	Bridging
Minor, no. (%)	(n=781)	(n=758)
Gastrointestinal	391 (50.1)	357 (47.1)
Cardiothoracic	139 (17.8)	151 (19.9)
Orthopedic	54 (6.9)	47 (6.2)
Urologic	41 (5.3)	45 (5.9)
Other	156 (19.9)	158 (20.9)
Major, no. (%)	(n=94)	(n=89)
Orthopedic	29 (30.9)	29 (32.6)
Urologic	26 (27.7)	20 (22.5)
General surgery	16 (17.0)	14 (15.7)
Other	23 (24.5)	26 (29.2)

*Initial classification of surgery/procedure not always aligned to bleeding risk designation.

Issues primaires

Outcome No. (%)	No Bridging (N = 918)	Bridging (N = 895)	P- value
ATE	4 (0.4)	3 (0.3)	0.01 (non-infer.) 0.73 (super.)
- stroke	2 (0.2)	3 (0.3)	
- TIA	2 (0.2)	0 (0)	
- systemic embolism	0 (0)	0 (0)	
Major bleeding	12 (1.3)	29 (3.2)	0.005 (super.)

- *Mean $CHADS_2$ in patients with TE event = 2.6 (range, 1-4)*
- *Median time to TE event = 19.0 days (IQR, 6.0-23.0)*
- *Median time to major bleed = 7.0 days (IQR, 4.0-18.0)*

Issues secondaires

Outcome No. (%)	No Bridging (N = 918)	Bridging (N = 895)	P-value
Death	5 (0.5)	4 (0.4)	0.88 (sup)
Myocardial infarction	7 (0.8)	14 (1.6)	0.10 (sup)
Deep vein thrombosis	0 (0)	1 (0.1)	0.25 (sup)
Pulmonary embolism	0 (0)	1 (0.1)	0.25 (sup)
Minor bleeding	110 (12.0)	187 (20.9)	<0.001 (sup)

Étude PAUSE

- Aim: To establish a safe, standardized protocol for the perioperative management of patients with atrial fibrillation (AF) who are taking a NOAC and need an elective surgery/procedure.
- Design: Multi-centre prospective cohort study
- Patients: 3,300 patients with AF (1,100 per NOAC)
- NOAC interruption interval: 4-5 half-lives (3-6% residual anticoagulant effect)

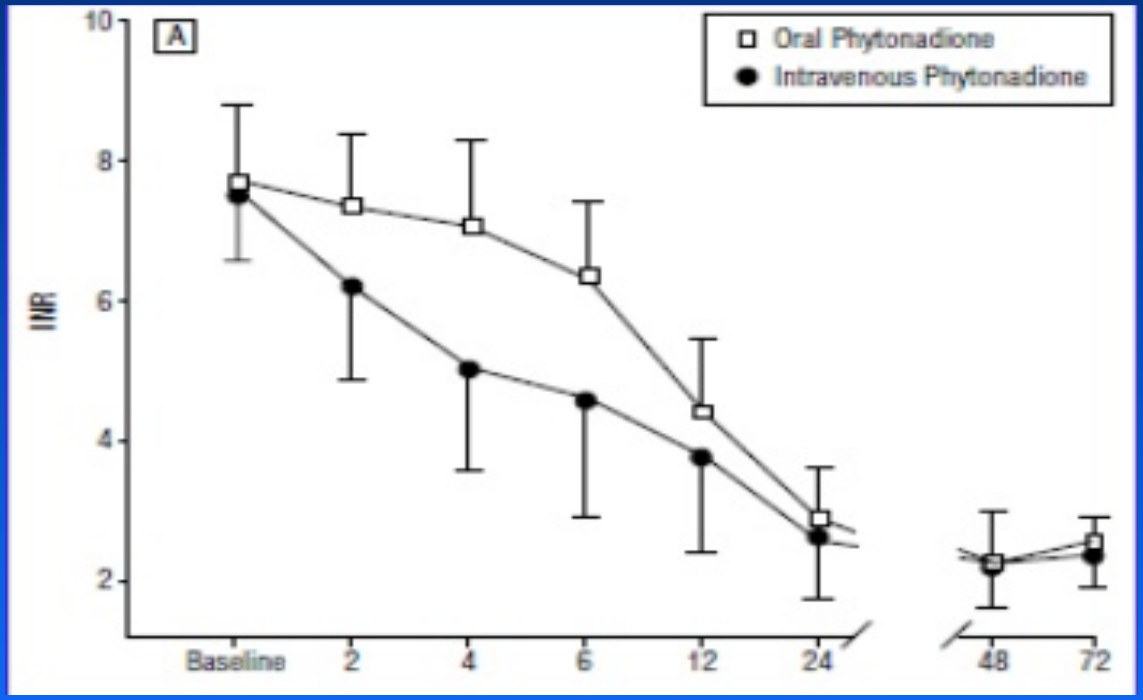
PAUSE Study

CIHR IRSC
Canadian Institutes of Health Research | Instituts de recherche en santé du Canada

HEART & STROKE FOUNDATION

VITAMINE K

	RIN >1,5 < 2,5	RIN > 2,5
CX < 24 HRES (Avec PCC)	0.5-1ou 2 mg IV	1-2.5/5 mg IV
CX > 24 HRES	0.5-2 mgs PO	1- 2.5 mgs PO



Vitamine K IV vs PO

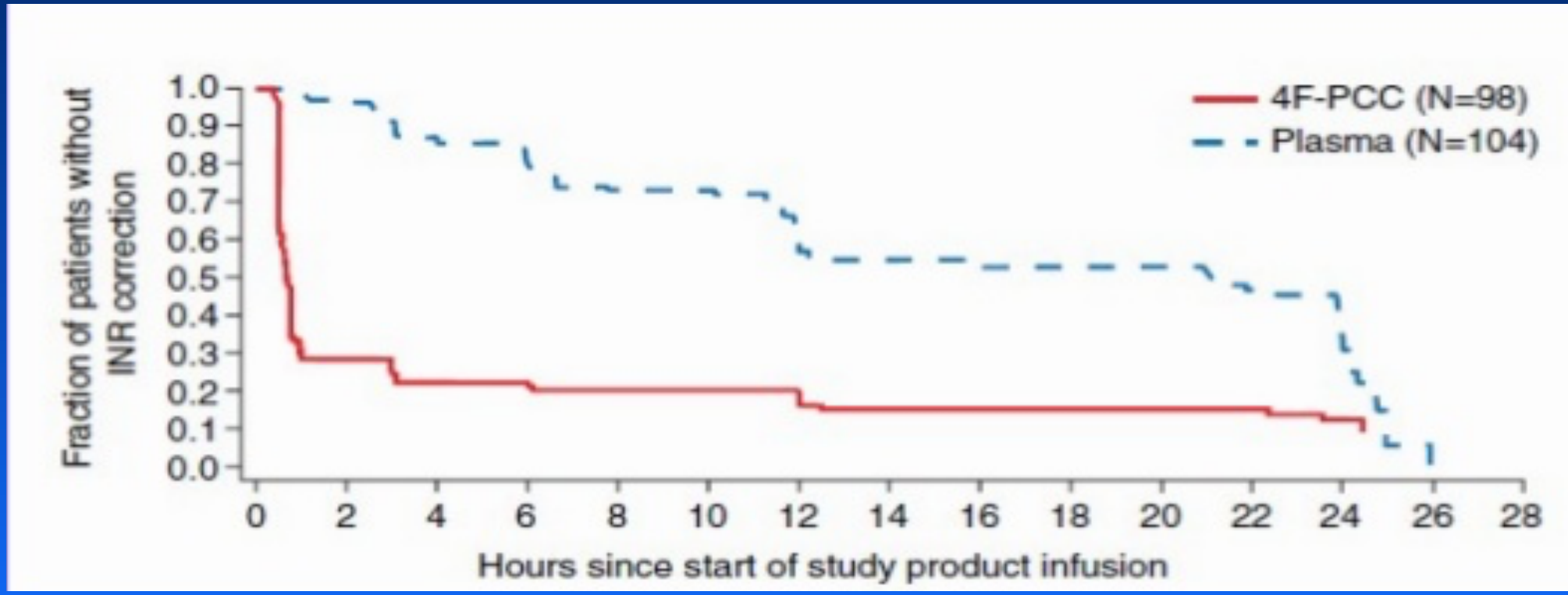
Lubetsky et al, Arch Int Med 2003

Complexes prothrombiniques

Beriplex™ ou Octaplex™

DOSES : 25-50 U/kgs selon RIN.
En général, poids max 100 kgs

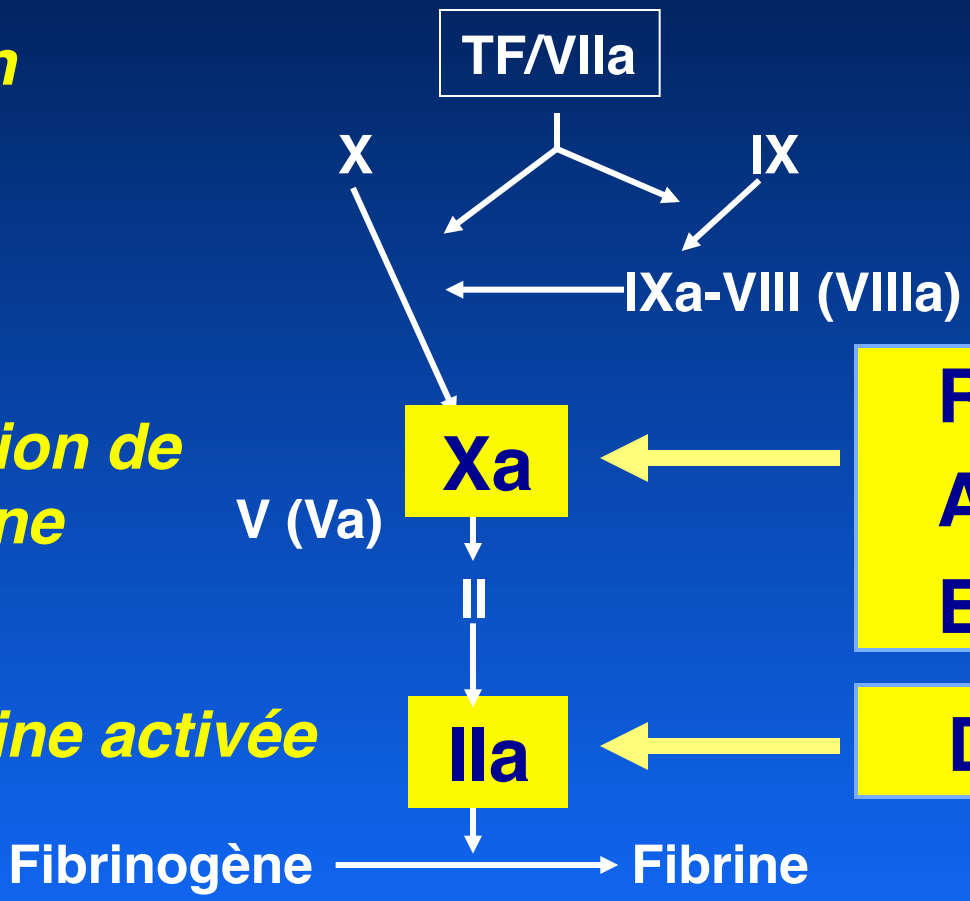
Correction du RIN : PCC vs PFC



Sarode et al, Circulation 2013

AOD pour la TEV et FA en 2016-2017

Cascade de coagulation



Rivaroxaban (Xarelto™)
Apixaban (Eliquis™)
Edoxaban (Lixiana™)

Dabigatran (Pradaxa™)

A. Roussin MD

Principes de base AOD
Gestion péri-procédurale

2 x demi-vie si procédure à faible risque de saignement

5 x demi-vie si procédure à risque modéré ou élevé de saignement (3-6% Rx résiduel ou moins)

Schulman-Crowther Blood 03-2012
Schulman et al Circulation 07-2015
ASRA Guidelines 2015
Spyropoulos, JTH 04-2016

PROCÉDURE

Risque de saignement *FAIBLE*

- Chirurgie dentaire (sauf extractions multiples)
- Cataractes
- Coronarographie et pose de PMP
- Ponction articulaire
- Biopsies cutanées
- Scopies sans biopsies
- Biopsie moëlle osseuse

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JVIR 2009 & uptodate 2016 & ACCP 2012

PROCÉDURE
Risque de saignement MODÉRÉ ou *ÉLEVÉ*

- Chirurgie majeure
- Drainage ou biopsie intraabdominal, retroperitonéal, thoracique
- Cholecystostomie percutanée
- Procédures endoscopiques avec biopsies
- Procédures spinales (vertébroplastie, épidurale, bloc facettaire)
  - ETC…...

JVIR 2009/ASRA2015

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Thérapie antithrombotique périopératoire

Risque thrombotique

Risk	Mechanical Heart Valve	Atrial fibrillation	VTE
High	•Any mitral •Older Aortic •< 6 mo. TIA or stroke	•$CHADS_2$ 5 or 6 •< 3 mo. TIA or stroke •Rheumatic valv. disease	•< 3 mo VTE •Severe thrombophilia
Moderate	•Bileaflet Aortic with one of following: AF, prior TIA or stroke, HBP, diabetes, CHF, age > 75	•$CHADS_2$ 3 or 4	•VTE 3 – 12 mo •Non severe thrombophilia •Recurrent VTE •Active cancer (Tx < 6 mo or palliative)
Low	•Bileaflet Aortic without AF and no other risk factor for stroke	•$CHADS_2$ 0 to 2 (and no prior TIA or stroke	Single VTE > 12 mo and no other risk factor

Principes de base AOD

Demi-vies selon fonction rénale

	Dabigatran (Pradaxa®)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)
Half-life:			
Mild renal impairment (CrCl ≥50mL/min))	7-17 hours	7-11 hours	8-12 hours
Moderate renal impairment (CrCl 30-49 mL/min)	17-20 hours	7-11 hours	8-12 hours
Severe renal impairment (CrCl <30 mL/min)	21-35 hours	11-15 hours	12-17 hours

Edoxaban (Lixiana™): 10-14 hours

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When to interrupt NOACs before surgery?

NOAC	Surgery Type	
	Low Bleed Risk	High Bleed Risk
dabigatran	(do not take NOAC on surgery day)	
- CrCl ≥50	*skip 1 day*	*skip 2 days*
- CrCl <50	*skip 2 days*	*skip 4 days*
rivaroxaban	*skip 1 day*	*skip 2 days*
apixaban	*skip 1 day*	*skip 2 days*

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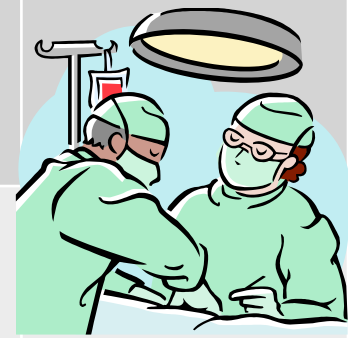
When to interrupt dabigatran?

High-bleed risk surgery/procedure (CrCl >50 mL/min)

Low-bleed risk surgery/procedure (CrCl >50 mL/min)

TIME	Thursday	Friday	Saturday	Sunday	Monday 1 PM
8 AM	✓	✓	✓	Ø	
6 PM	✓	✓	✓	Ø	

24h 48h 67h

dabigatran half-life = 12-14 hrs, 80% renal clearance

When to interrupt dabigatran (CrCl <50 mL/min)?

High-bleed risk surgery/procedure

Low-bleed risk surgery/procedure

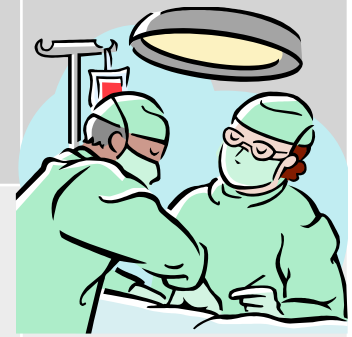
TIME	Thursday	Friday	Saturday	Sunday	Monday (surgery)
AM	✓	✓	Ø	Ø	
PM	✓	✓	Ø	Ø	

dabigatran half-life = 12-14 hrs, 80% renal clearance

When to interrupt apixaban?

High-bleed risk surgery/procedure

Low-bleed risk surgery/procedure

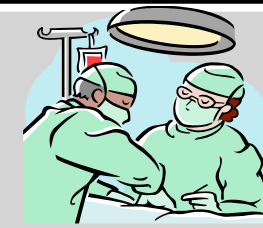
TIME	Thursday	Friday	Saturday	Sunday	Monday (surgery)
8 AM	✓	✓	✓	Ø	
6 PM	✓	✓	✓	Ø	

apixaban half-life = 8-12 hrs, 25% renal clearance

When to interrupt rivaroxaban?

High-bleed risk surgery/procedure

Low-bleed risk surgery/procedure

TIME	Thursday	Friday	Saturday	Sunday	Monday (surgery)
AM	✓	✓	✓ ø	ø	

rivaroxaban half-life = 9-12 hrs, 33% renal clearance

DABIGATRAN et chirurgie selon le risque de saignement

Nombre de jours d'arrêt pré-opératoire

Before Invasive Procedures Such as Elective Surgery in Patients R… …ice-Daily Dosing With a Standa…

1 - 2 - 4

Saignement

Clearance

Renal Function (Creatinine Clearance), mL/min	Half-Life, h*	Timing of Discontinuation of Dabigatran Before Surgery: Standard Risk of Bleeding	Timing of Discontinuation of Dabigatran Before Surgery: High Risk of Bleeding†
>80	13 (11–22)	24 h	2–4 d
>50–≤80	15 (12–34)	24 h	2–4 d
>30–≤50	18 (13–23)	≥2 d (48 h)	4 d
≤30	27 (22–35)	2–5 d	>5 d

Adapté de: Hankey Gj, Eikelboom JW. Circulation 2011; 123: 1436-1450

Et monographie PRADAXA 2012

A Roussin MD

RIVAROXABAN et chirurgie selon le risque de saignement

Nombre de jours d'arrêt pré-opératoire

Selon le risque de saignement

Adapté de: Monographie XARELTO 2013

APIXABAN et chirurgie selon le risque de saignement

Nombre de jours d'arrêt pré-opératoire

1 à 2 au moins

Selon le risque de saignement

Adapté de: Monographie ELIQUIS 2012

Gestion post-opératoire des AOD

Pas de « bridging» proposé sauf si NPO/iléus/Vo

La prophylaxie antithrombotique reste requise: HNF sc ou HBPM sc

Reprise prudente des NACOs:

Début action rapide: 24-72 hres post-op

Considérer demi-dose post-op si risque thrombotique élevé et risque hémorragique élevé
Ex.: Pradaxa™ 75 mgs BID, Xarelto™ 10 mgs po die, Eliquis™ 2.5 mgs BID

Schulman-Crowther Blood 03-2012
Schulman et al Circulation 07-2015
ASRA Guidelines 2015
Spyropoulos, JTH 04-2016

2015 ASRA Guideline Recommendations for Interventional Spine and Pain Procedure

- *"We recommend a 5 half-life interval between discontinuation of a NOAC and a medium- to high-risk procedure."*

- *"If the risk of VTE is high, we recommend LMWH bridging during the stoppage of the NOAC with the LMWH discontinued 24 hours before the procedure."*

- *"We could not provide strength and grading of recommendations as there are not enough well-designed studies concerning interventional pain procedures to support such grading."*

Narouze S, et al. *Reg Anesth Pain Med* 2015

2015 ASRA Guidelines on Perioperative NOAC Management

Narouze S, et al. *Reg Anesth Pain Med* 2015;40:182

NOAC	Interruption Interval	Post-op Resumption
dabigatran	4-6 days	24 hrs
apixaban	3-5 days	24 hrs
rivaroxaban	3 days	24 hrs

Procédures spinales
AOD

TABLE 4. Recommended Intervals Between Discontinuation of the New Anticoagulants and Interventional Pain Procedure and Between the Procedure and Resumption of the New Anticoagulants

Drug	Half-life	Recommended Interval Between Discontinuation of Drug and Interventional Pain Procedure* (5 Half-lives)†‡	Recommended Interval Between Procedure and Resumption of Drug
Dabigatran	12–17 h	4–5 d	24 h
	28 h (renal disease)	6 d (renal disease)	
Rivaroxaban	9–13 h	3 d	24 h
Apixaban	15.2 ± 8.5 h	3–5 d‡	24 h

*The procedures include medium- and high-risk interventional pain procedures. For low-risk procedures, a shared decision making should be followed, a 2 half-life interval may be considered.

†Because of the lack of published studies and in view of the added risks involved in patients with spine abnormalities, we took the upper limit of the half-life of each drug in calculating the 5 half-lives.

Adapté ASRA guidelines 2015

Permutations AVK et AOD

- **AVK vers AOD:**
  - Cesser AVK et débuter AOD 48 heures après
    - Surtout si CHADS ≥ 5 ou TEV < 3 mois
      - Donc sauter 2 jours et débuter le 3ème jour
    - AOD 72 heures après si CHADS ≤ 4 ou TEV > 3 mois
    - *Option: vérifier si RIN < 2 (principe sous-jacent)*

Doser INR pré-AOD

- **AOD vers AVK:**
  - Débuter AVK et cesser AOD au 4-5ème jours si RIN > 2
    - *Même principe qu'avec HNF et HBPM pour TEV*

A. Roussin MD

Filtres VCI: ACCP 2016

Role of Inferior Vena Cava Filter in Addition to Anticoagulation for Acute DVT or PE

17. In patients with acute DVT or PE who are treated with anticoagulants, we recommend against the use of an inferior vena cava (IVC) filter (Grade 1B).

TABLE 16] Summary of Findings: Temporary IVC Filter vs No Temporary IVC Filter in Addition to Anticoagulation for Acute DVT or PE[a,b]

PREPIC 2

Outcomes	No. of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects	
				Risk With No Temporary IVC Filter in Addition to Anticoagulation	Risk Difference with Temporary IVC Filter (95% CI)
All-cause mortality	399 (1 study) 3 mo	⊕⊖⊕⊖ **Moderate**[c,d] because of imprecision	RR 1.25 (0.6-2.6)	60 per 1,000	15 more per 1,000 (from 24 fewer to 96 more)
Recurrent PE	399 (1 study) 3 mo	⊕⊖⊕⊖ **Moderate**[c,d] because of imprecision	RR 2.00 (0.51-7.89)	15 per 1,000	15 more per 1,000 (from 7 fewer to 104 more)
Major bleeding	399 (1 study) 3 mo	⊕⊖⊕⊖ **Moderate**[c,d] because of imprecision	RR 0.80 (0.32-1.98)	50 per 1,000	10 fewer per 1,000 (from 34 fewer to 49 more)

Filtres VCI
Les indications

- Il n'y a qu'une indication "absolue": EP avec TVP proximale chez un patient ne pouvant recevoir un AC

- Les autres "indications" sont relatives:
  - comme par exemple EP massive thrombolysée en phase aigue
  - ou EP sous-segmentaire unique avec TVP distale ne pouvant recevoir un AC

Filtres VCI
La durée de AC après le retrait du filtre

- CAS: patiente 62 ans AVC et TVP il y a 6 mois: filtre VCI et warfarine administrée pour 3 mois puis cessée. Vue au 6ème mois; retrait du filtre alors tenté sans succès.

- L'interniste soupèse les options:
  - Reprendre AC long terme, n'importe lequel
  - Considérer un AOD dont l'apixaban 2.5 BID
  - Considérer un AC pour 12 mois
  - Considérer AAS
  - Ne pas reprendre l'AC

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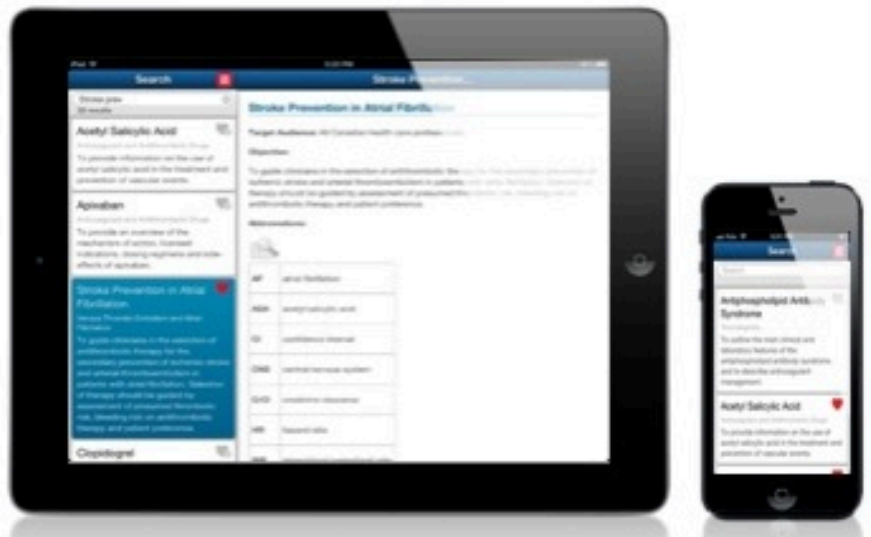

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Acetyl Salicylic Acid (ASA)

Anticoagulant & Antiplatelet Drugs, Heart & Arterial Diseases

To provide information on the use of acetyl salicylic acid in the prevention of vascular thromboembolic events.

Apixaban (Eliquis®)

Anticoagulant & Antiplatelet Drugs, Atrial Fibrillation, NOACs/DOACs, Venous Thromboembolism

To provide an overview of the mechanism of action, licensed indications, dosing regimens and side-effects of apixaban.

Cancer and Thrombosis

Venous Thromboembolism

To assist health care professionals in the management of cancer-associated thrombosis (CAT).

Central Venous Catheter-Related Deep Vein Thrombosis

Venous Thromboembolism

To provide guidance on the diagnosis, treatment and prevention of central venous catheter-related deep vein thrombosis (DVT).

Clopidogrel (Plavix®)

Anticoagulant & Antiplatelet Drugs, Heart & Arterial Diseases

To describe the clinical pharmacology and therapeutic application of clopidogrel, and to discuss drug dosing, duration of therapy, genetic polymorphisms affecting drug metabolism, and potential drug interactions with proton pump inhibitors.

Dabigatran (Pradaxa®)

Anticoagulant & Antiplatelet Drugs, Atrial Fibrillation, NOACs/DOACs, Venous Thromboembolism

To provide an overview of the mechanism of action, licensed indications, dosing regimens, and side-effects of dabigatran.

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New/Novel Oral Anticoagulants (NOACs): Coagulation Tests

Anticoagulant & Antiplatelet Drugs, NOACs/DOACs, Perioperative management

To describe the effect of the new/novel direct oral anticoagulants (NOACs) on laboratory coagulation tests which are widely available: prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT), and thrombin clotting time (TCT), and to discuss how clinicians should use and interpret coagulation tests in patients taking a NOAC who are bleeding or require elective surgery or an invasive procedure.

New/Novel Oral Anticoagulants (NOACs): Comparison and Frequently-Asked Questions

Anticoagulant & Antiplatelet Drugs, Atrial Fibrillation, NOACs/DOACs

To provide a comparison of the new/novel oral anticoagulants (NOACs) currently available in Canada, and to address frequently-asked questions regarding NOACs.

New/Novel Oral Anticoagulants (NOACs): Management of Bleeding

Anticoagulant & Antiplatelet Drugs, NOACs/DOACs

To assist clinicians in the management of bleeding in patients receiving direct oral anticoagulants (NOACs).

New/Novel Oral Anticoagulants (NOACs): Peri-Operative Management

NOACs/DOACs, Perioperative management

To provide guidance for the peri-operative management of patients who are receiving a new/novel oral anticoagulant (NOAC) and require an elective surgery/procedure. (For guidance on management of patients who require an urgent or emergency surgery/procedure, please refer to the Perioperative Anticoagulant Management Algorithm.)

Références: "App"

www.thrombosiscanada.ca

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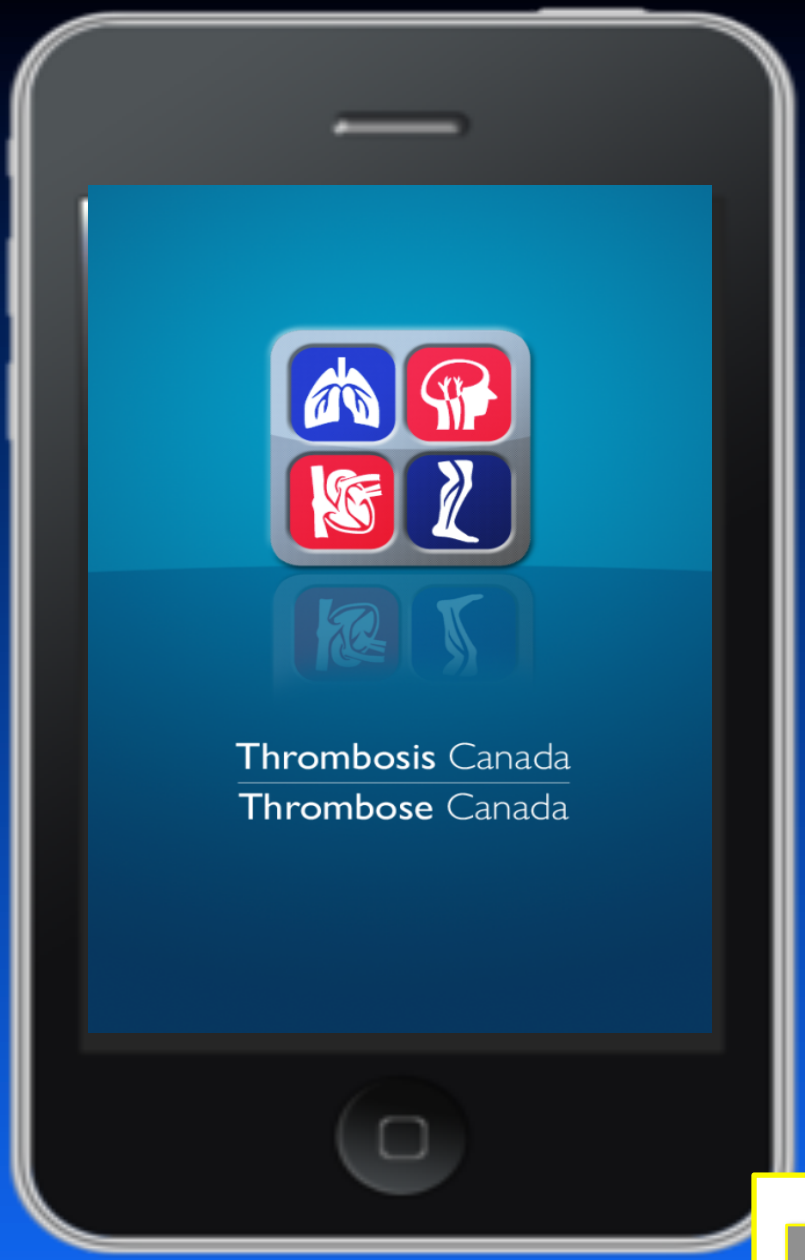

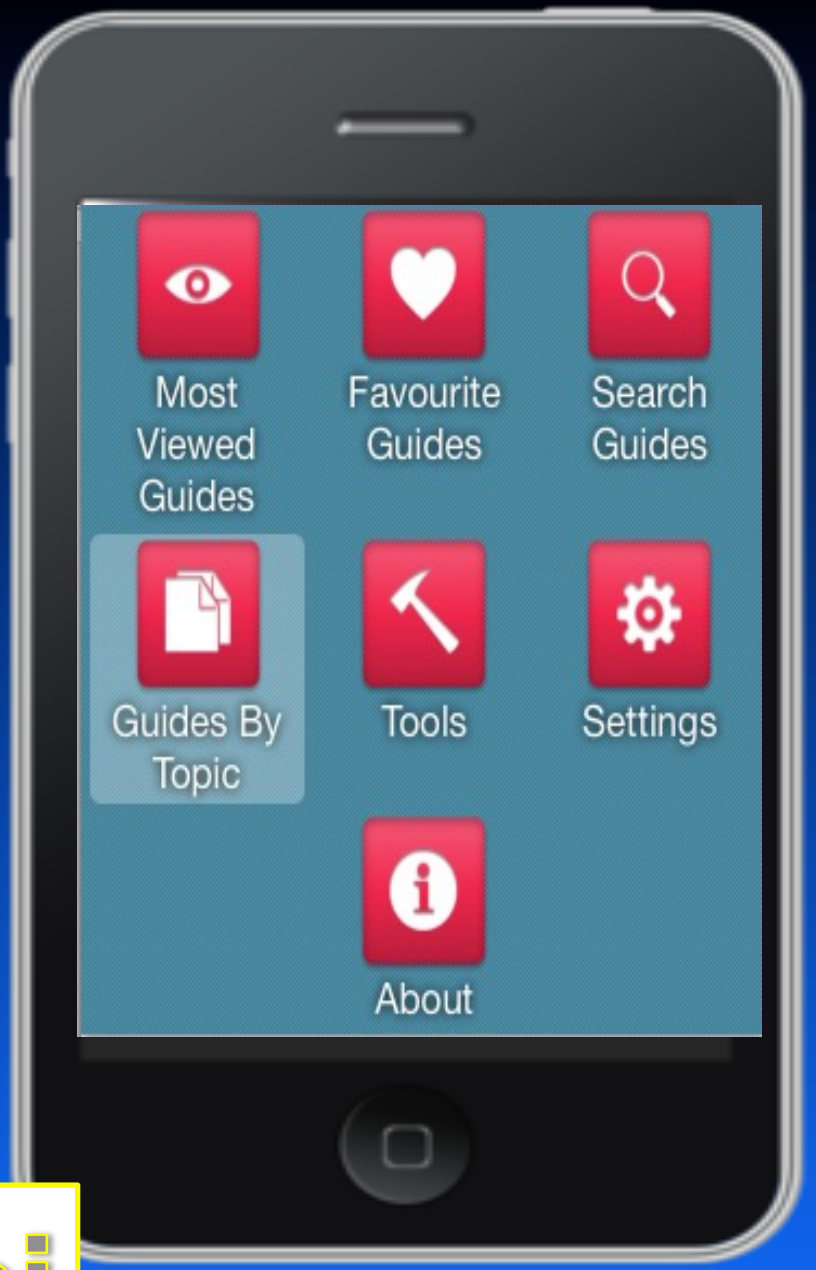

Merci

A Roussin