

Lignes directrices TEV ACCP 2016

16^{ème} congrès annuel SSVQ

- ◆ Sélection appropriée du traitement selon la situation
 - ◆ Durée de l'anticoagulation
- ◆ Thrombolyse et thérapies endovasculaires

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CANVECTOR

- Funded by CIHR-ICRH and various partners (including **SSVQ**) in 2015-2020
- \$5.2 M in total
- Co-Directors: Susan Kahn (McGill) & Rodger (U Ottawa)



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

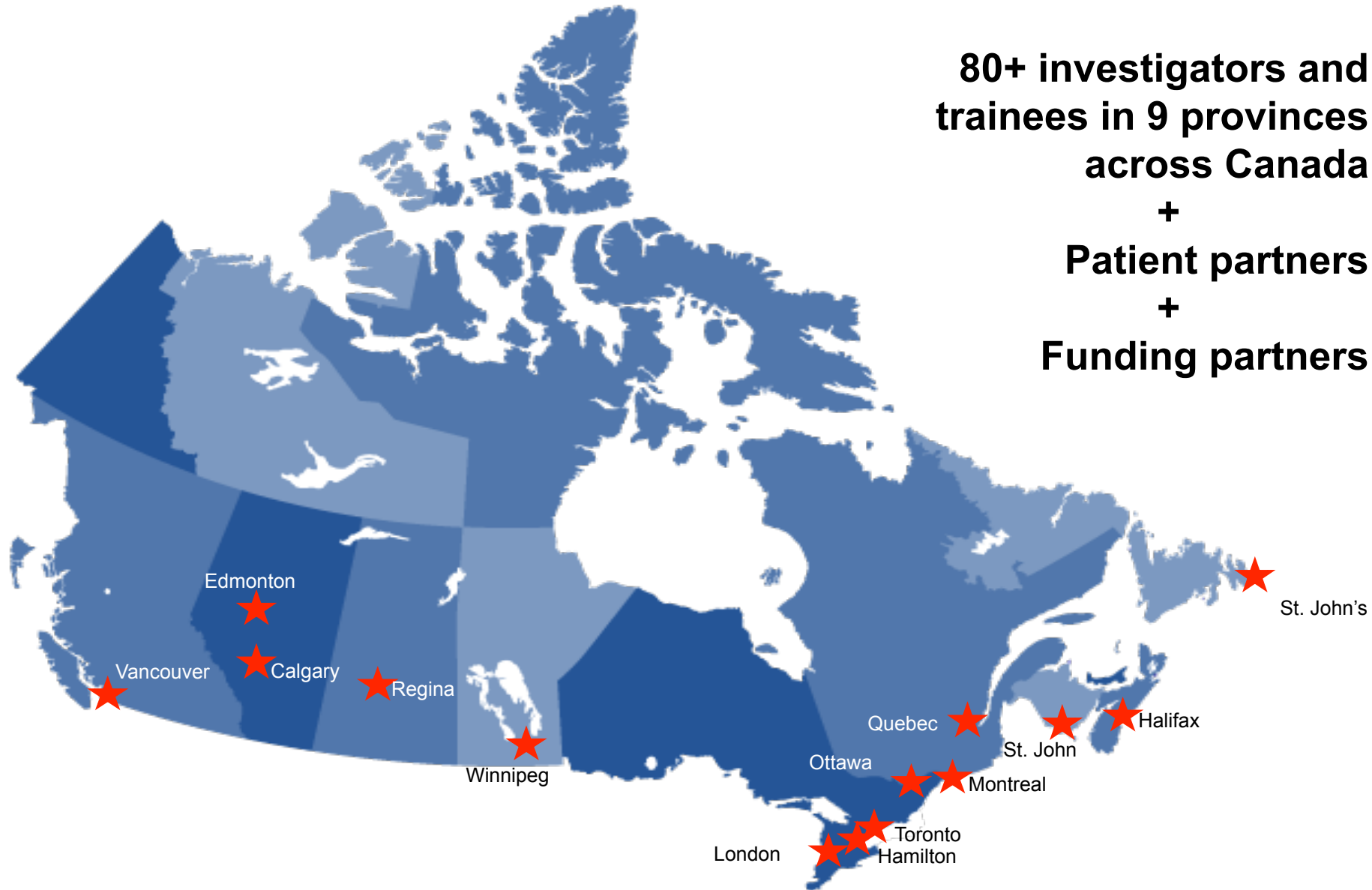


CANVECTOR

Who are we?

VTE-focused research & training network

**80+ investigators and
trainees in 9 provinces
across Canada
+
Patient partners
+
Funding partners**





Our mission

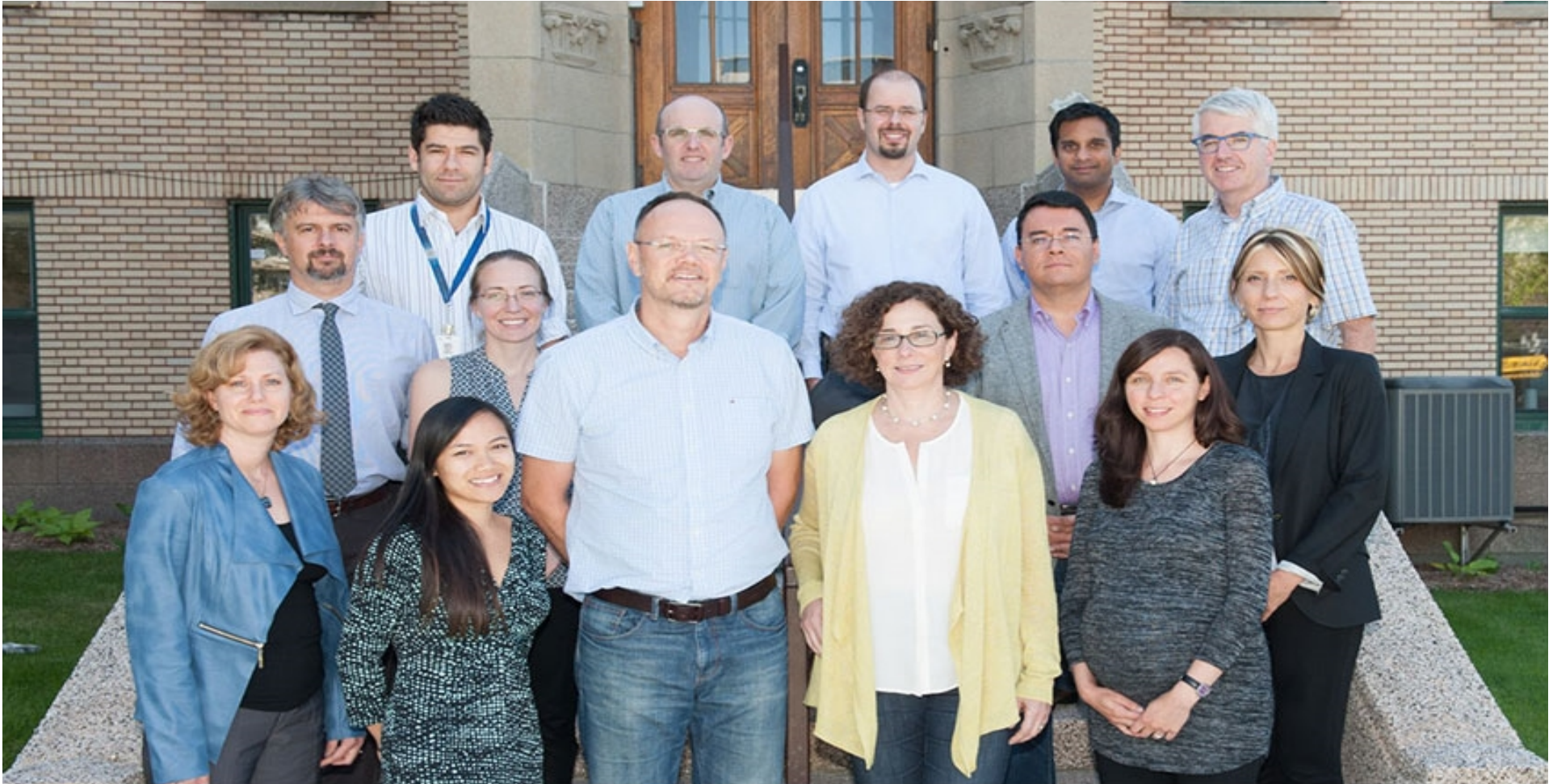
To decrease the health, social and economic burden of VTE on affected individuals, their families, and on Canadians as a whole.

Our vision

To create an enduring, pan-Canadian network of stakeholders, researchers, methodology experts, knowledge transfer experts, research trainees, clinical research professionals, industry partners, public agency partners, healthcare providers, and patient groups whose combined efforts:

- reduce VTE occurrence
- improve VTE diagnosis and therapeutic management
- improve the safety of anticoagulant delivery
- enhance the quality of life of those impacted by VTE, both in Canada and globally

The CanVECTOR Scientific Steering Committee



Pictured left to right:

Front row – Nicole Langlois (Admin), Charlotte Guzman (Admin), Marc Rodger, Susan Kahn, Jessica Emed

Middle row – Alfonso Iorio, Lisa Duffett, Alejandro Lazo-Langner, Vicky Tagalakis

Last row – David Morrison (Admin - Finance), Gregoire Le Gal, Marc Carrier, Sudeep Shivakumar, Clive Kearon.

Not pictured – Jeffrey Weitz, Ed Conway, James Douketis, and patient partners (TBD)



CANVECTOR

Check us out:

www.canvector.ca

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Feel free to contact us:

info@canvector.ca

Lignes directrices TEV ACCP 2016

Conflits d'intérêts potentiels 2014 à 2016

Aviseur expert ou comités aviseurs:

Bayer, BI, BMS, Leo, Merck, Pfizer, Sanofi

Fonds de recherche:

Astra-Zeneca et Bayer

Conférencier:

Bayer, BI, BMS, Leo, Merck, Pfizer et Sanofi

Options de traitement de la TEV: ACCP/AT 10

Warfarine, HNF, HBPM et AOD

Warfarine

HBPM s.-c. ou
HNF i.v. ou s.-c. ou
fondaparinux s.-c.

Traitement de transition (5-10 jours) offrant
un effet AC immédiat

Warfarine RIN 2-3, voie orale plutôt que HBPM 2C

HBPM
Plutôt que AVQ
2B ou AOD 2C

CANCER, (6 mois...) HBPM en monothérapie

AOD
Plutôt que AVK
2B

Rivaroxaban 15 mg BID durant 21 jours, puis à 20 mg DIE

HBPM (HNF) durant 5-10 jours, puis dabigatran 150/110 mg BID

Apixaban 10 mg BID durant 7 jours, puis 5 mg BID 6 mois puis 2.5 mg BID

Cas spéciaux - HNF

HNF, voie s.-c. si CrCl < 30 mL/min, risque accru de
saignement, si le patient a besoin d'un réversibilité rapide
ou si un traitement thrombolytique est envisagé

Options de traitement de la TEV

AOD et INESSS 2016

Code CV 157 pour TVP
6 mois
Si warfarine problématique

Code CV 165 pour EP
long terme
Si warfarine problématique

AOD

Rivaroxaban 15 mg BID durant 21 jours, puis 20 mg DIE

HBPM (HNF) durant 5-10 jours, puis dabigatran 150/110 mg BID

Apixaban 10 mg BID durant 7 jours, puis 5 mg BID 6 mois puis 2.5 mg BID

Code CV 169 pour TEV (TVP et EP)
6 mois

Code CV 170 pour TEV
Après 6 mois pour 12 mois

AT 10 ACCP/CHEST 2016

EP sous-segmentaire

*19. In patients with subsegmental PE (no involvement of more proximal pulmonary arteries) and

no proximal DVT in the legs who have a

(i) **low risk for recurrent VTE** (see text), we suggest clinical surveillance over anticoagulation (Grade 2C) or

(ii) **high risk for recurrent VTE** (see text), we suggest anticoagulation over clinical surveillance

(Grade 2C).



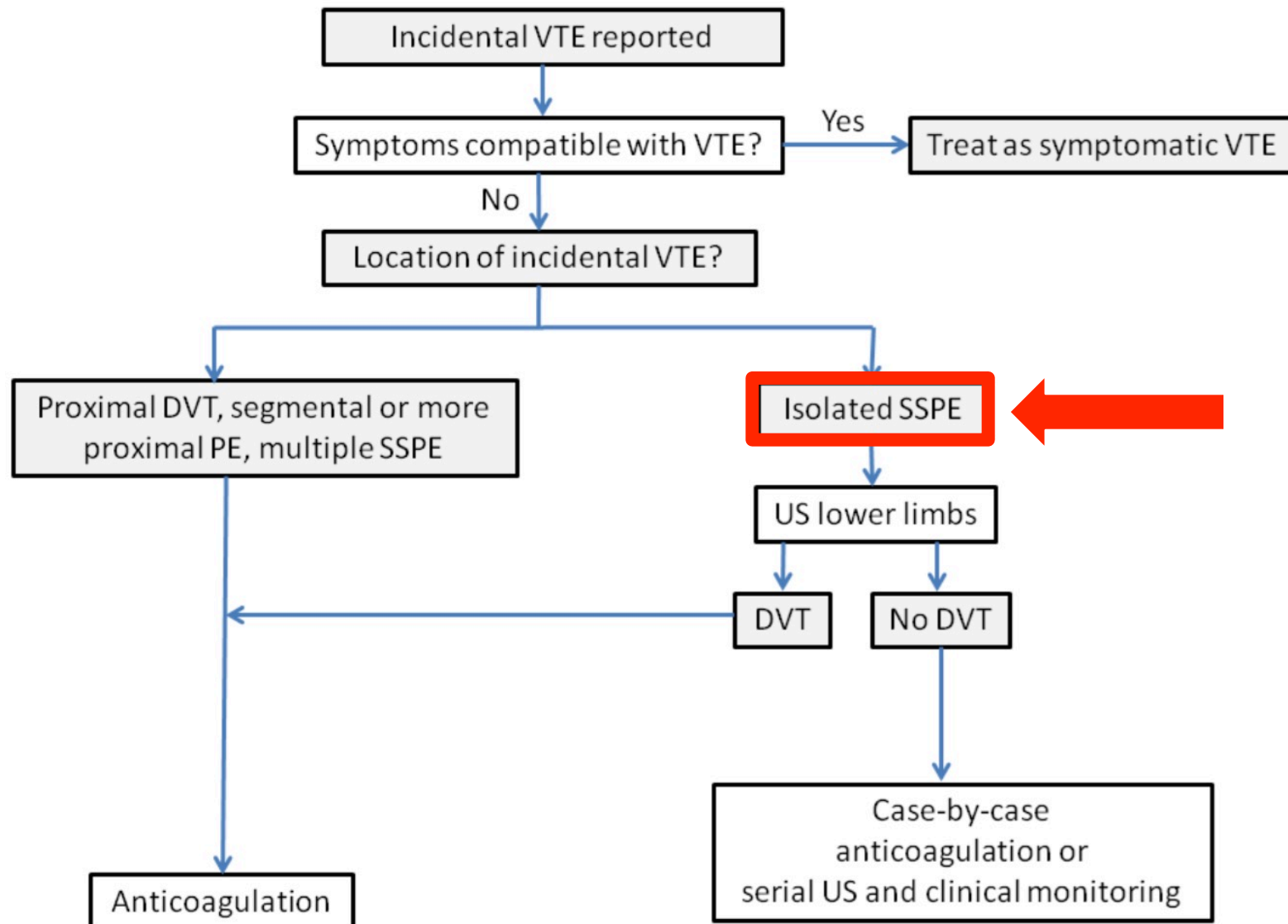
Echo prox...



Cancer...

Diagnostic et traitement de la TEV fortuite

Patients oncologiques: *Guide de SSC de ISTH 2015*



Risque de récurrence de TEV, saignement majeur et mortalité pour l'EP fortuite traitée ou non

Annalyse regroupé de 926 patients avec cancer

- ◆ Saignements majeurs avec AVK 3 fois plus que HBPM
- ◆ Risque égal de récurrence pour EP fortuite sous-segmentaire vs EP fortuite proximale
- ◆ HBPM mieux que AVK
- ◆ Thérapie équivalente pour EP sous-segmentaire vs proximale.

AT 10 ACCP/CHEST 2012-2016

TVP mollet

13. In patients with **acute isolated distal DVT** of the leg and (i) without severe symptoms or risk factors for extension (see text), we suggest serial imaging of the deep veins for 2 weeks over anticoagulation (Grade 2C) or (ii) with severe symptoms or risk factors for extension (see text), we suggest anticoagulation over serial imaging of the deep veins (Grade 2C)

Extension proximale \pm 15%
Problème de faux + avec écho

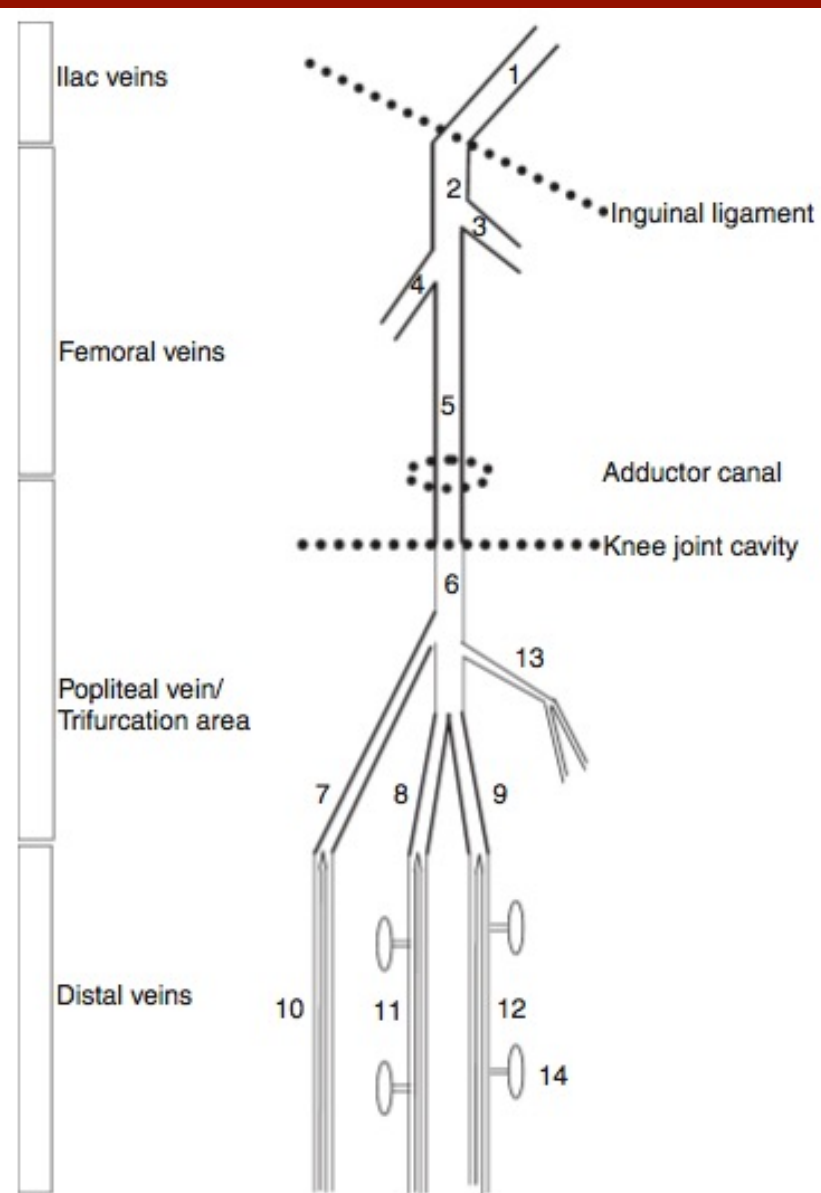
AT 10 ACCP/CHEST 2016

TVP mollet: facteurs de risque pour extension

- ◆ D-dimère positif (surtout si très élevé sans autre cause évidente)
- ◆ Thrombose extensive (eg, >5 cm longueur, plusieurs veines touchées, >7 mm de diamètre)
- ◆ Thrombose près des veines proximales
- ◆ Pas de facteur de risque réversible de thrombose
- ◆ Cancer actif
- ◆ Historique de TEV
- ◆ Patient hospitalisé

TVP distale

Terminologie et anatomie



Veines du mollet

7 et 10: tibiales antérieures

8 et 11: tibiales postérieures

9 et 12: péronières

13: jumelles

14: soléaires

**Veines
"profondes"**

**Veines
"musculaires"**

TVP mollet

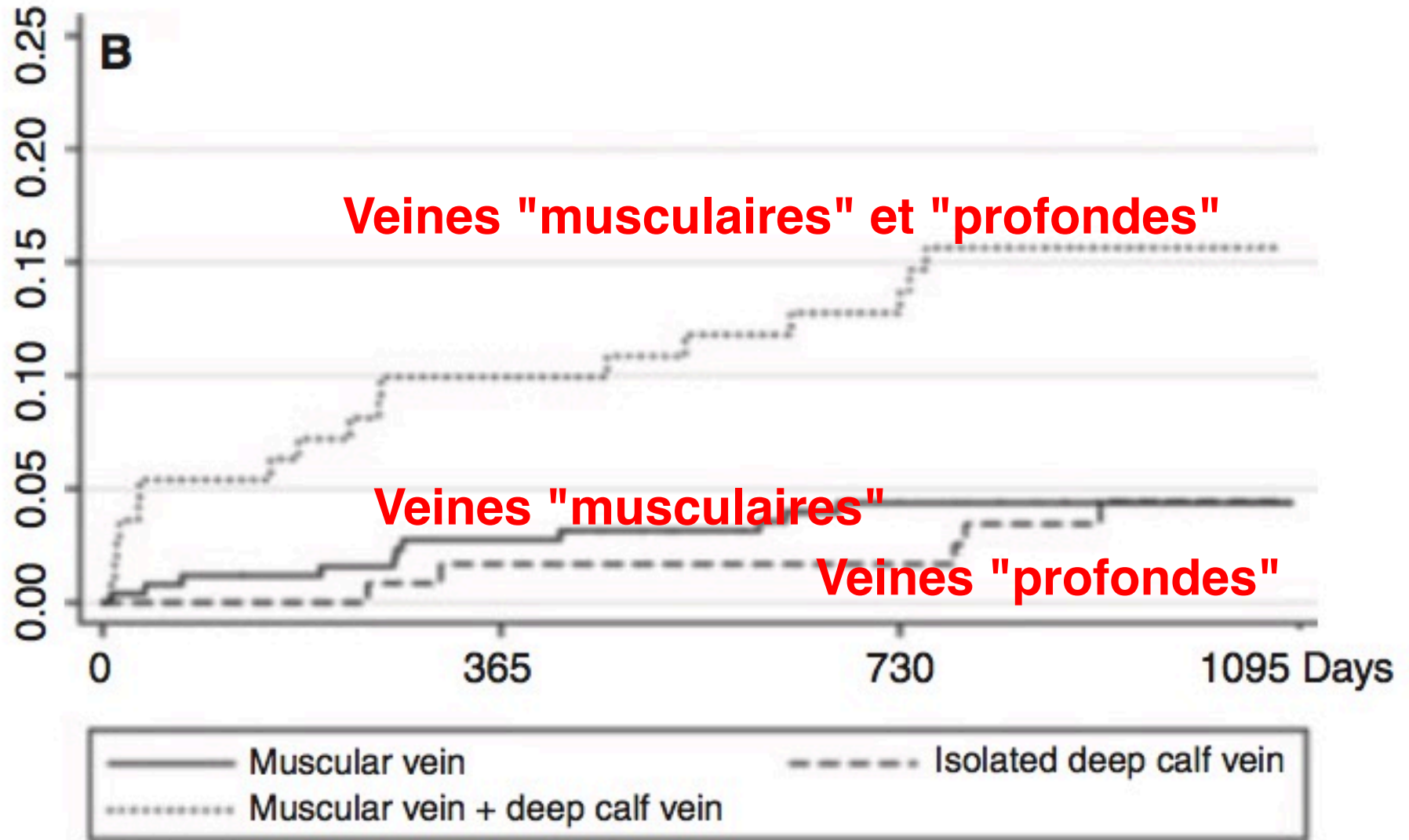
Facteurs prédictifs échographiques de récurrence

Table 3 Predictive factors and incidence of VTE recurrence after stopping anticoagulants in the case of isolated distal DVT (univariate and multivariate analyses, incidence of VTE recurrence)

	Univariate analysis, HR (95% CI)	Multivariate analysis, HR (95% CI)*	Incidence of VTE recurrence, % PY (95% CI)
Ultrasonographic characteristics of index DVT			
Number of venous segments thrombosed			
● Single unilateral thrombosis (ref)	–	–	1.8 (1.1–2.9)
● Multiple unilateral thromboses	–2.4 (1.1–5.0)†	–2.9 (1.4–6.1)	4.9 (3.1–7.8)
● Bilateral DVT	4.8 (1.8–13.3)†	4.0 (1.4–11.1)	8.9 (3.7–21.4)

TVP du mollet: veines profondes et musculaires

Incidence de récurrence après l'arrêt des AC



AT 10 ACCP/CHEST 2012-2016

TVP mollet: échos sériés (1 et 2 sem.)

15. In patients with **acute, isolated, distal DVT** of the leg who are managed with serial imaging, we

- (i) recommend no anticoagulation if the thrombus does not extend (Grade 1B),
- (ii) suggest anticoagulation if the thrombus extends but remains confined to the distal veins (Grade 2C), and
- (iii) recommend anticoagulation if the thrombus extends into the proximal veins (Grade 1B).

Fardeau des échos répétés

AT 10 ACCP/CHEST 2016

Thérapie initiale sans cancer

***2. In patients with DVT of the leg or PE and no cancer, as long-term (first 3 months) anticoagulant therapy, we suggest dabigatran, rivaroxaban, apixaban, or edoxaban over vitamin K antagonist (VKA) therapy (all Grade 2B).**

Moins de saignements, plus pratique...

AT 10 ACCP/CHEST 2016

TEV récurrente sous AVK ou AOD

***29. In patients who have recurrent VTE on VKA therapy (in the therapeutic range) or on dabigatran, rivaroxaban, apixaban, or edoxaban (and are believed to be compliant), we suggest switching to treatment with LMWH at least temporarily (Grade 2C)**

Évaluer récurrence, compliance, cancer etc.

Au moins 1 mois

AT 10 ACCP/CHEST 2016

TEV récurrente sous HBPM

***30. In patients who have recurrent VTE on long term LMWH (and are believed to be compliant), we suggest increasing the dose of LMWH by about one-quarter to one-third (Grade 2C).**

Évaluer récurrence, compliance, cancer etc.

Augmenter dose HBPM de 30%

AT10 et TEV: durée de l'anticoagulation

Selon facteurs provoquants dont la présence de cancer

Situation	Recommandations	Grade
<u>TVP proximale ou EP <i>provoquées</i></u> (asympto. ou non) <ul style="list-style-type: none">• Facteur de risque chirurgical• Facteur de risque non chirurgical transitoire	3 mois minimum 3 mois 3 mois	1B 1B 2B
<u>TVP proximale ou EP <i>non provoquées</i></u> <ul style="list-style-type: none">• Risque de saignement bas ou modéré• Risque de saignement élevé	• Thérapie long terme • 3 mois	2B 1B
<u>TEV avec cancer actif</u> (<i>Tx < 6 mois ou persistant</i>) <ul style="list-style-type: none">• Risque de saignement non élevé• Risque de saignement élevé	• Thérapie long terme • Thérapie long terme	1B 2B

Risque de récurrence:
Risque relatif

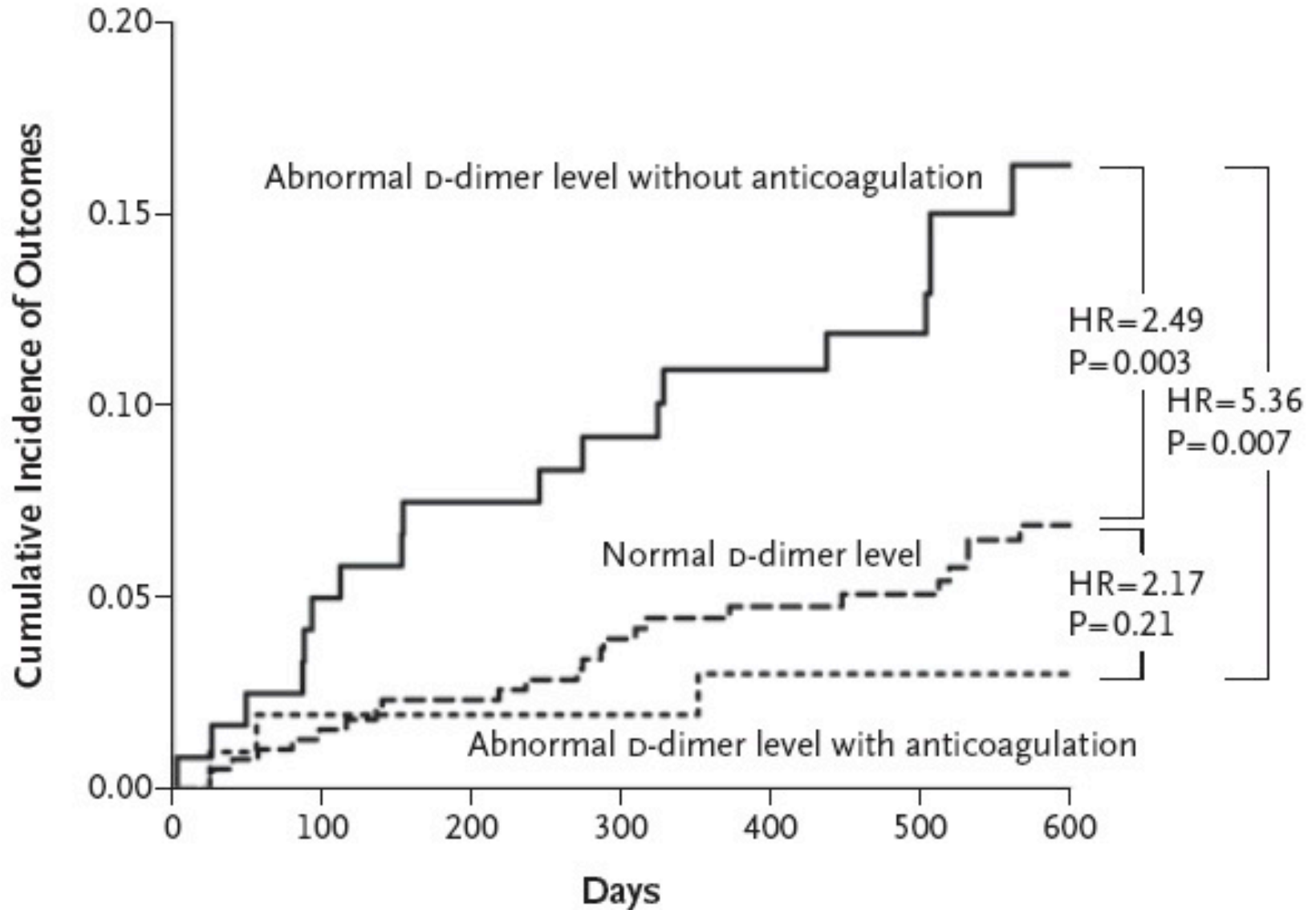
- D-Dimère neg. 1 mois après l'arrêt AVK: .5
ü surtout utile chez les femmes
- Homme (par rapport à une femme): 1.7

Risque de récurrence de TEV et D-Dimère

608 pts

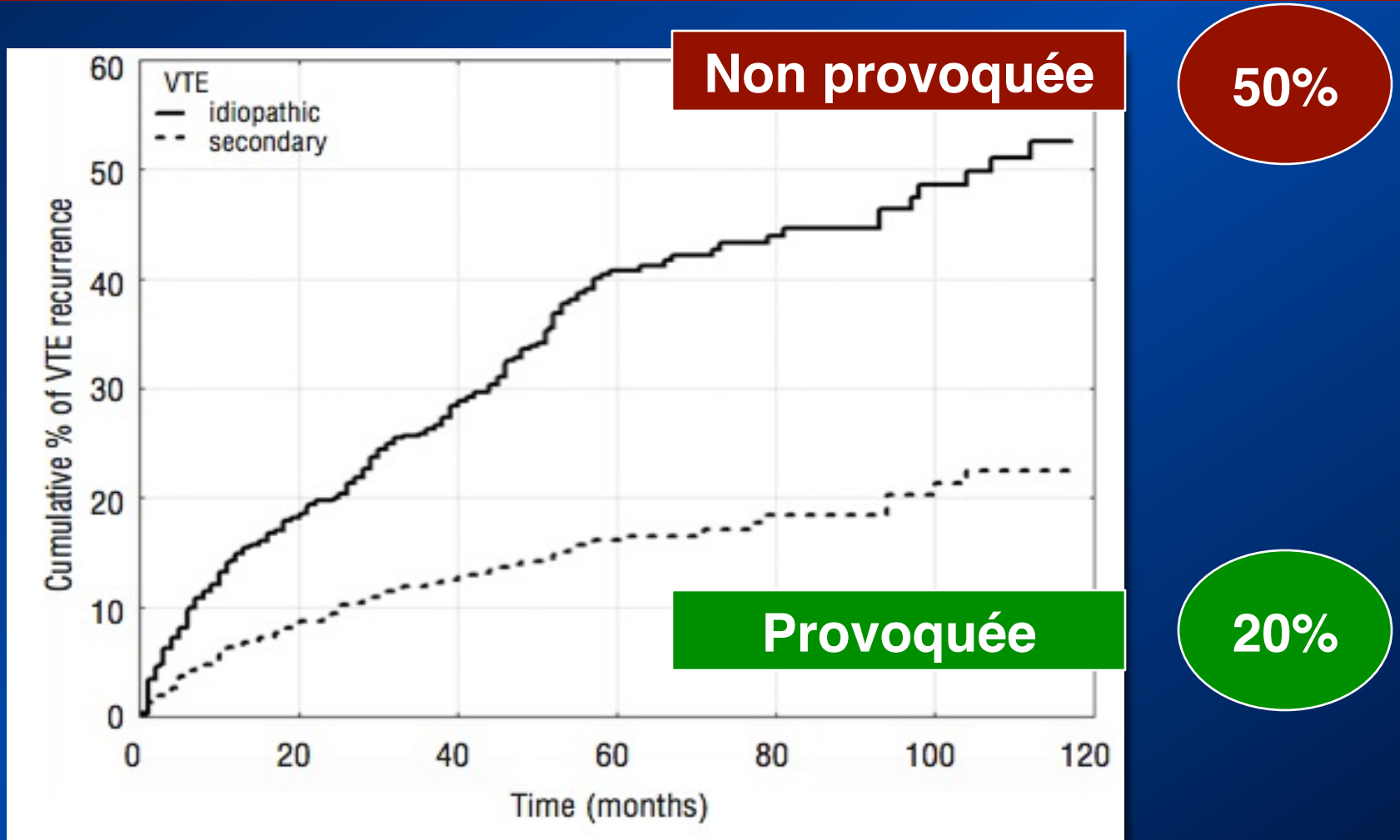
DD pos:
36.7% pts

Suivi:
1.4 an



TEV: incidence cumulative

Provoquée VS non provoquée à 10 ans



Risque de récurrence: rôle d'une thrombophilie isolée

Études rétro. et prospectives, la plupart non randomisées

Antithrombin, protéin C ou S	10-17% / 1 ^{ère} année Puis 2.7% / an
Facteur V Leiden homozygote Antiphospholipide (APS)	48% / 4 ans 29 à 53% / 4-5 ans
Facteur VIII Hyperhomocystéinémie Facteur V Leiden hétérozygote Mutation II G20210A	RR 6.7 ! RR 2.7 RR 1.0 à 4.7 RR 1.0 à 4.9
Facteur IX, XI	?

Synergie des facteurs de risque

V Leiden et Contraceptif oral

Facteur de risque	RR	Incidence annuelle
Nil	1	0.8 / 10 000
CO	4	3.0 / 10 000
V Leiden	7	5.7 / 10 000
CO + V Leiden	35	28.5 / 10 000

Combined oral contraceptives, thrombophilia and the risk of venous thromboembolism: a systematic review and meta-analysis

- We performed a meta-analysis on thrombosis risk in thrombophilic oral contraceptive (COC)-users.
- The results support discouraging COC-use in women with a natural anticoagulant deficiency.
- Contrary, additive risk of factor V Leiden (FVL) or prothrombin-G20210A (PT) mutation is modest.
- Women with a FVL/PT-mutation as single risk factor can use COCs if alternatives are not tolerated.

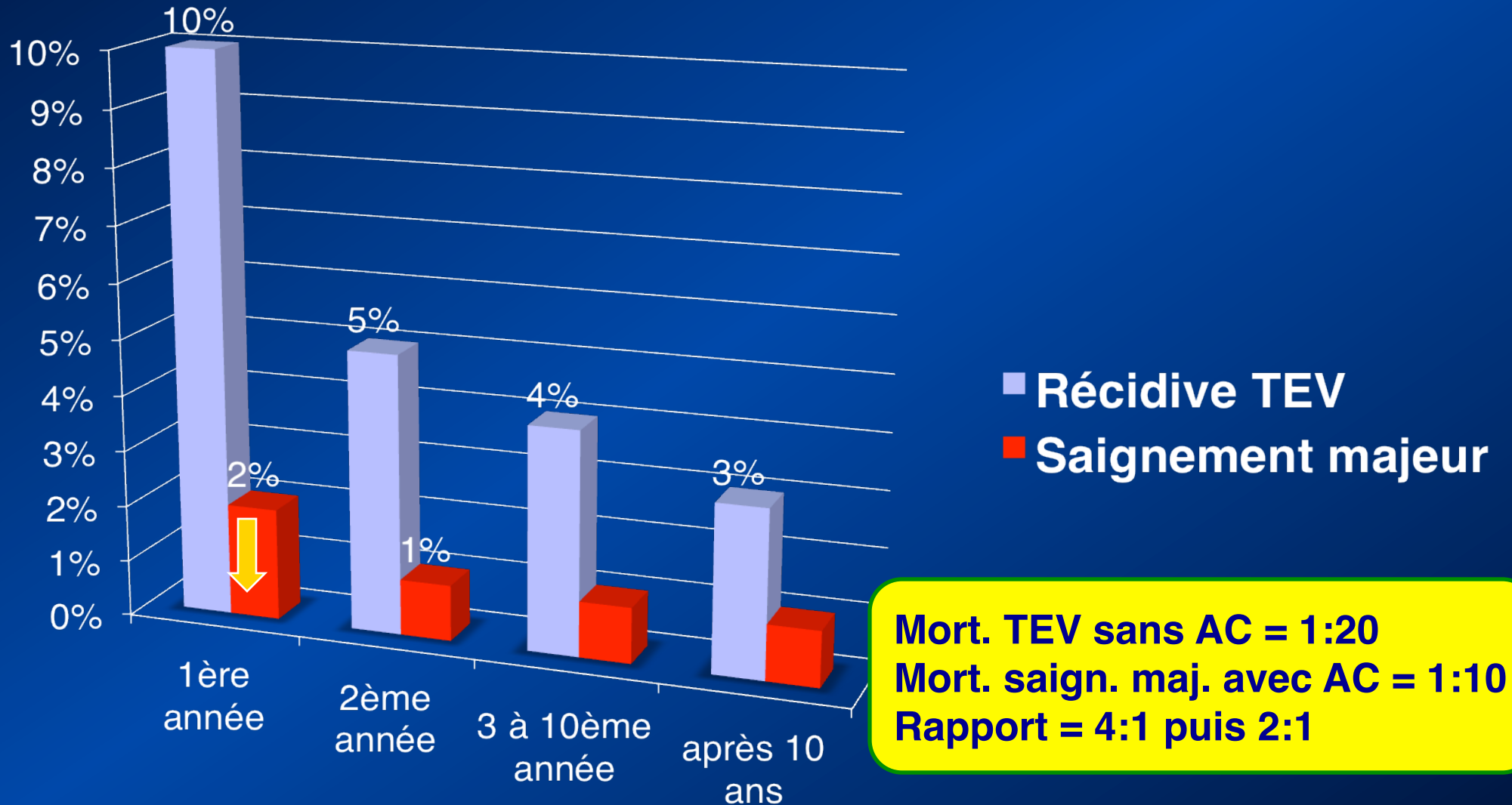
AT 10 ACCP/CHEST 2016

TEV thérapie prolongée, selon le risque de saignement

*9. In patients with a first VTE that is an unprovoked proximal DVT of the leg or PE and who have a (i) **low or moderate bleeding risk** (see text), we suggest extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 2B), and a (ii) **high bleeding risk** (see text), we recommend 3 months of anticoagulant therapy over extended therapy (no scheduled stop date) (Grade 1B).

Sexe et D-dimère...

TEV non provoquée risque annuel de récurrence En fonction du risque de saignement majeur



Étude REVERSE (Suivi à 8 mois)

Étude prospective de marqueurs potentiels de récurrence

◆ 9.3% récurrence annuelle de TEV:

➔ 13.7% hommes

➔ 5.5% femmes

◆ Analyse multivariée: 5 règles hommes, 2 femmes

➔ Aucune règle utile pour hommes

➔ **HERDOO2** validé pour femmes

Étude REVERSE (Suivi à 8 mois)

Étude prospective de marqueurs potentiels de récurrence

“Men continue and HERDOO2”

1. **Men Continue**

2. Women: 1 or less discontinued

3. **Women: with 2 or more continue**

HERDOO2 Predictors:

➔ **H**yperpigmentation, **E**dema or **R**edness (**HER**)

➔ Vidas **D**-Dimer >250 on AC

➔ **O**besity- BMI >30 or

➔ **O**lder than age65

# of risk factors	Annual risk of VTE
0-1	1.6%
2 or more	14.1%

Étude REVERSE

Suivi 5.1 années APRÈS arrêt AC

Risque annuel de récurrence	Hommes	Femmes
647 patients (âge moyen 53; ♀ 49%)	4.9%	
Hommes	7.4%	
Femmes haut risque HERDOO2 \geq 2 points		5.9%
Femmes bas risque HERDOO2 \leq 1 points		1.1%
Hommes HER + ("Hyperpigmentation, OMI, Redness")	10.6%	
Femmes HER +		6%

Étude REVERSE II

HERDOO2 évalué après 5 à 12 mois d'AC

Récidive de TEV à 1 an 2,779 patients (âge moyen 54.4)	Hommes	Femmes
Hommes et femmes haut risque* qui cessent AC (*HERDOO2 \geq 2 points)	8.1%	
Hommes et femmes haut risque* qui continuent AC (*HERDOO2 \geq 2 points) 1,534 hommes et 591 femmes	1.6%	
Femmes bas risque* qui cessent AC (*HERDOO2 \leq 1 points) 622 femmes		3%
Femmes post-ménopausées âgées > 50 Même si HERDOO2 \leq 1 points		5.7%

AT 10 ACCP/CHEST 2016

AAS

*12. In patients with an unprovoked proximal DVT or PE who are stopping anticoagulant therapy and do not have a contraindication to aspirin, we suggest aspirin over no aspirin to prevent recurrent VTE (Grade 2C).

Mieux que rien...

AT 10 ACCP/CHEST 2016

EP et thérapie ambulatoire

*20. In patients with low-risk PE and whose home circumstances are adequate, we suggest treatment at home or early discharge over standard discharge (eg, after first 5 days of treatment) Q9 (Grade 2B).

Sélection: Score PESI

AT 10 ACCP/CHEST 2016

EP grave sans hypotension

*22. In most patients with acute PE not associated with hypotension, we recommend against systemically administered thrombolytic therapy (Grade 1B)

Suivi serré des SV...

AT 10 ACCP/CHEST 2016

EP importante qui se détériore

*23. In selected patients with acute PE who deteriorate after starting anticoagulant therapy but have yet to develop hypotension and who have a low bleeding risk, we suggest systemically administered thrombolytic therapy over no such therapy (Grade 2C).

D'où l'importance de la surveillance

AT 10 ACCP/CHEST 2016

EP importante et thrombolyse

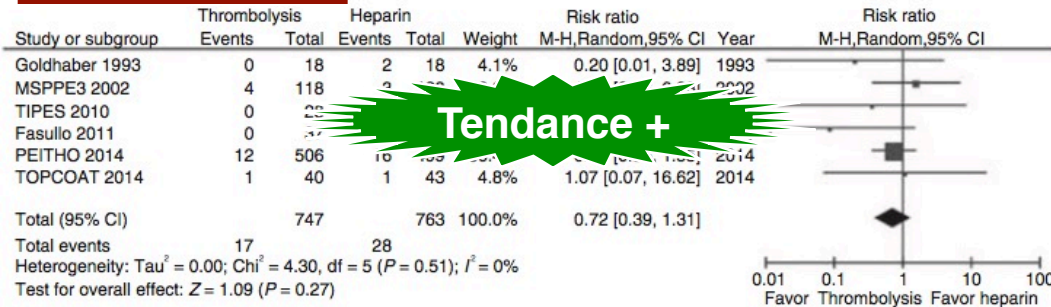
*24. In patients with acute PE who are treated with a thrombolytic agent, we suggest systemic thrombolytic therapy using a peripheral vein over catheter directed thrombolysis (CDT) (Grade 2C).

Selon expertise locale

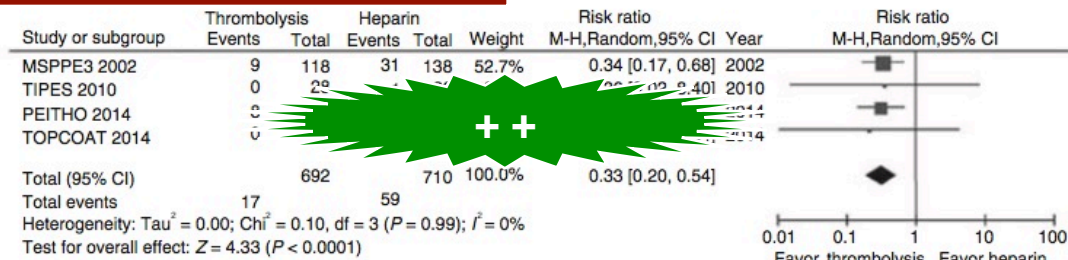
Thrombolyse systémique pour l'EP sub-massive

Méta-analyse: efficacité, saignements et détérioration

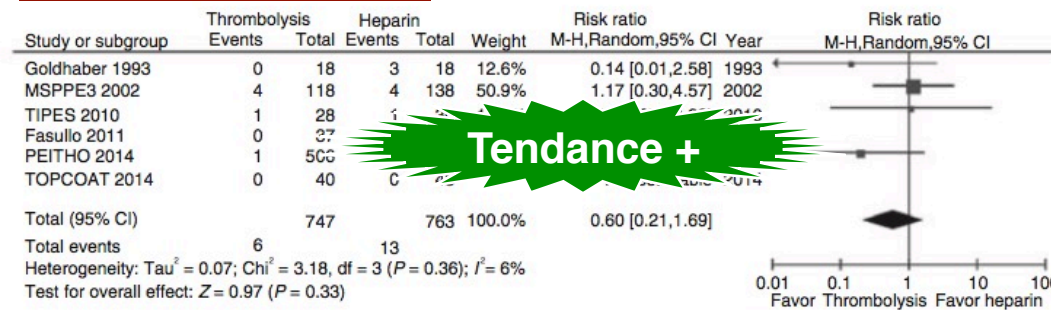
Mortalité



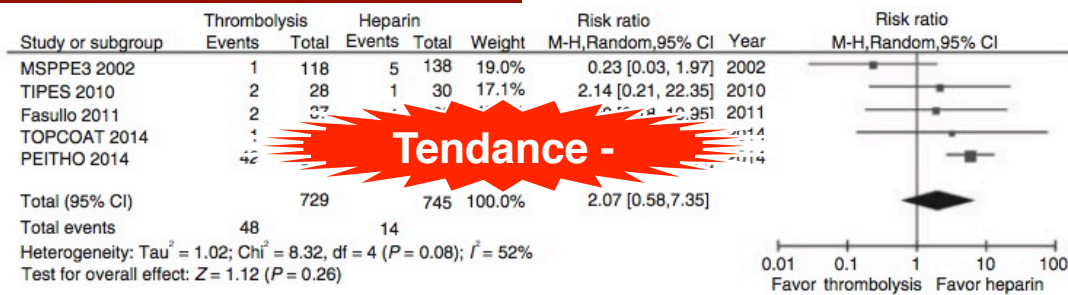
Détérioration clinique



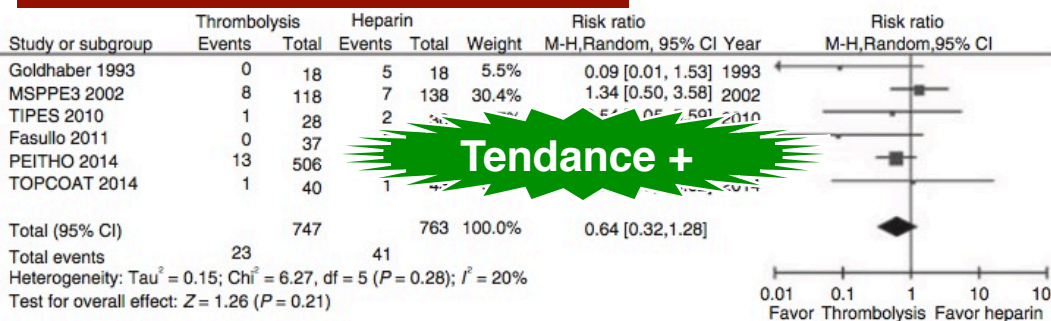
Récidive EP



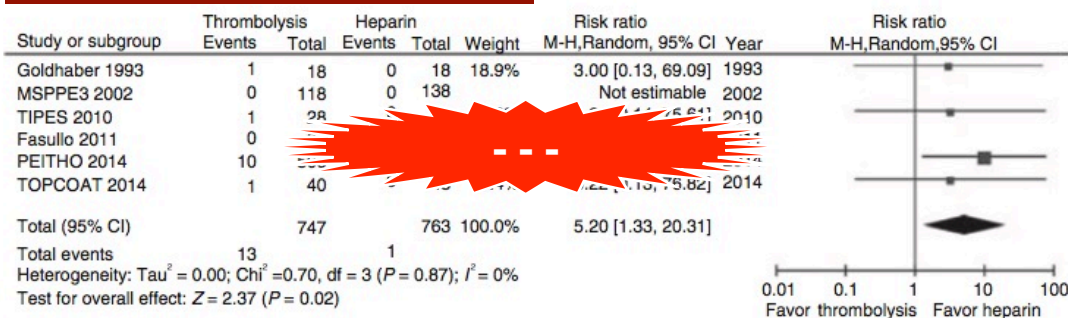
Saignements majeurs



Récidive EP et Mortalité



Saignements intra-crâniens



Thrombolyse systémique pour l'EP aigue

Méta-analyse: efficacité et saignements majeurs

Table 2 Efficacy outcomes, subgroup analyses

	All studies			Studies including ^a High-risk PE	Intermediate-risk PE	Low and intermediate-risk PE	Group difference
	OR (95% CI)	P-value	I ² (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)	P-value
Mortality	0.59 (0.36 to 0.96)	0.034	0	0.48 (0.20 to 1.15)	0.42 (0.17 to 1.03)	0.96 (0.41 to 2.24)	0.36
PE mortality	0.29 (0.14 to 0.60)	<0.001	0	0.15 (0.03 to 0.78)	0.17 (0.05 to 0.67)	0.63 (0.20 to 1.97)	0.23
Death or treatment escalation	0.34 (0.22 to 0.52)	<0.001	0	0.18 (0.04 to 0.79)	0.37 (0.20 to 0.69)	0.35 (0.18 to 0.66)	0.67
PE recurrence	0.50 (0.27 to 0.94)	0.031	0	0.97 (0.31 to 2.98)	0.25 (0.06 to 1.03)	0.46 (0.17 to 1.21)	0.33

Table 3 Safety outcomes, subgroup analyses

	All studies			Alteplase	Tenecteplase	Other thrombolytics	Group difference
	OR (95% CI)	P-value	I ² (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)	P-value
Major bleeding	2.91 (1.95 to 4.36)	<0.001	25	1.07 (0.43 to 2.62)	5.02 (2.72 to 9.26)	2.16 (1.03 to 4.54)	0.02
Fatal/intracranial haemorrhage	3.18 (1.25 to 8.11)	0.008	0	1.09 (0.27 to 4.40)	7.32 (1.64 to 32.63)	NA	0.07

AT 10 ACCP/CHEST 2012-2016

Thrombolyse par catheter pour TVP M. Inf. aigue proximale

16. In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over CDT (Grade 2C)

En 2016: "The CAVENT Study has since reported that CDT reduced PTS, did not alter quality of life, and appears to be cost-effective"

"our results together with the ATTRACT trial and the CAVA trial could provide definitive evidence for the use of catheter-directed thrombolysis in the treatment of severe proximal DVT"

AT 10 ACCP/CHEST 2016

Thrombolyse par catheter pour TVP M. inf. aigue proximale

- ◆ A retrospective analysis found that CDT (3649 patients) was associated with an increase in transfusion (twofold), intracranial bleeding (threefold), PE (1.5-fold), and vena caval filter insertion (twofold); long-term outcomes and PTS were not reported.



- ◆ A single-center prospective registry found that US-assisted CDT in acute iliofemoral (87 patients) achieved high rates of venous patency, was rarely associated with bleeding, and that only 6% of patients had PTS at 1 year.



AT 10 ACCP/CHEST 2016

Contre-indications à la thrombolyse locale ou systémique

Major Contraindications^a

- Structural intracranial disease
- Previous intracranial hemorrhage
- Ischemic stroke within 3 mo
- Active bleeding
- Recent brain or spinal surgery
- Recent head trauma with fracture or brain injury
- Bleeding diathesis

Relative contraindications^b

- Systolic BP >180
- Diastolic BP >110
- Recent bleeding (nonintracranial)
- Recent surgery
- Recent invasive procedure
- Ischemic stroke more than 3 mo previously
- Anticoagulated (eg, VKA therapy)
- Traumatic cardiopulmonary resuscitation
- Pericarditis or pericardial fluid
- Diabetic retinopathy
- Pregnancy
- Age >75 y
- Low body weight (eg, <60 kg)
- Female
- Black race

Thrombose veineuse profonde

Thrombolyse par cathéter

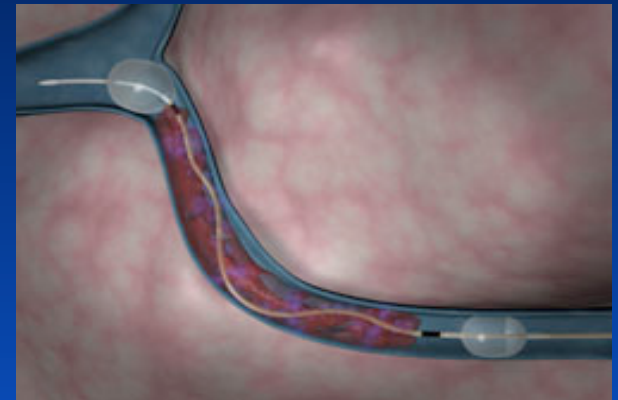
Exemples de types de perfusions

Perfusion

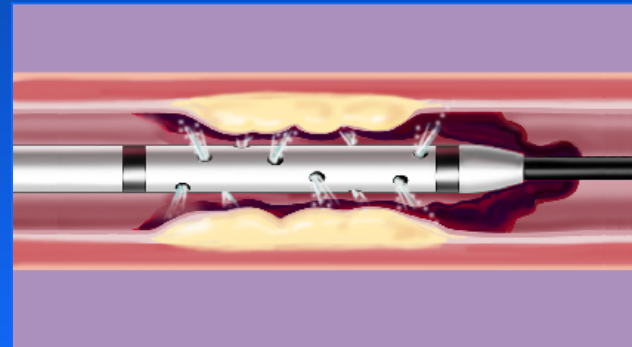
Pharmaco-mécanique



Trellis™



Angiojet™



EKOS™



AT 10 ACCP/CHEST 2016

Thromboendarterectomie pour le traitement de l'hypertension pulmonaire chronique

***26. In selected patients with chronic thromboembolic pulmonary hypertension (CTEPH) who are identified by an experienced thromboendarterectomy team, we suggest pulmonary thromboendarterectomy over no pulmonary thromboendarterectomy (Grade 2C).**

Dans les centres d'expertise

AT 10 ACCP/CHEST 2012-2016

Thrombolyse pour la TVP du membre supérieur

27. In patients with acute upper extremity DVT (UEDVT) that involves the axillary or more proximal veins, we suggest anticoagulant therapy alone over thrombolysis (Grade 2C).

28. In patients with UEDVT who undergo thrombolysis, we recommend the same intensity and duration of anticoagulant therapy as in patients with UEDVT who do not undergo thrombolysis (Grade 1B).

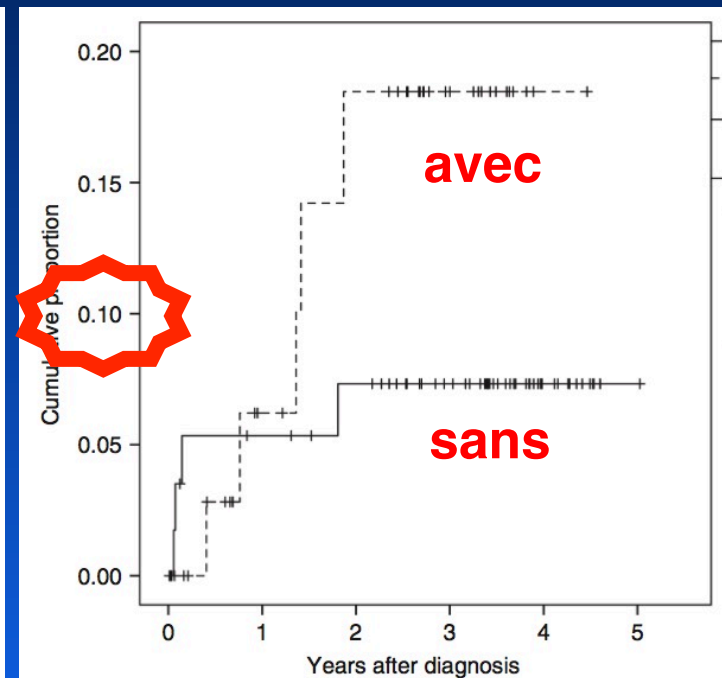
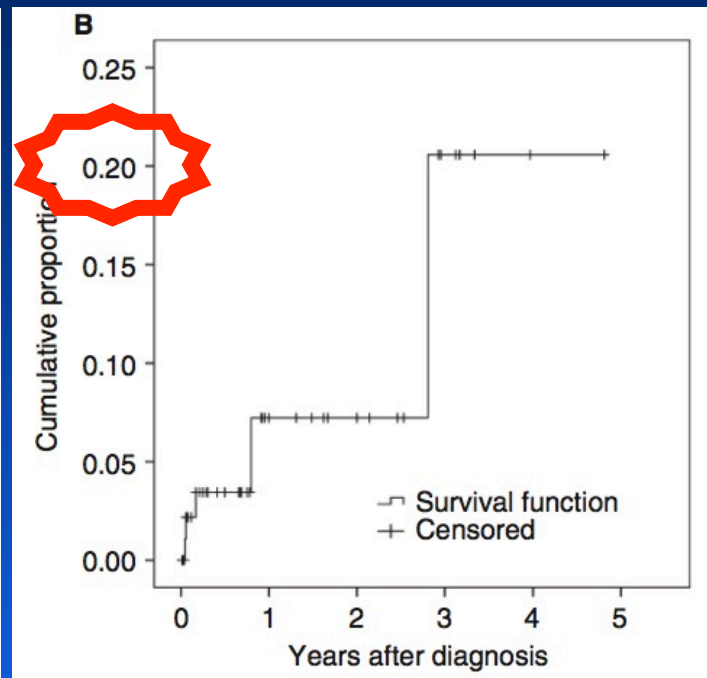
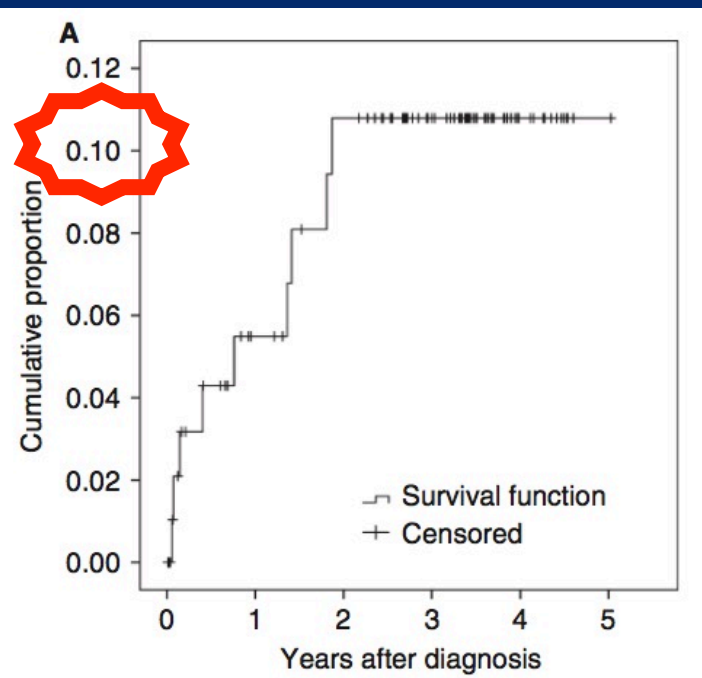
TVP du membre supérieur

Récidive de TEV vs saignements majeurs

Risque de récurrence de TEV

Risque de saignement majeur

Risque de récurrence de TEV
Avec ou sans cancer



Apixaban (Eliquis®)

Anticoagulant & Antiplatelet Drugs, Atrial Fibrillation, Novel Oral Anticoagulants, 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).

Dabigatran (Pradaxa®)

Anticoagulant & Antiplatelet Drugs, Atrial Fibrillation, Novel Oral Anticoagulants, Venous Thromboembolism

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

Deep Vein Thrombosis (DVT): Diagnosis

Venous Thromboembolism

To provide an evidenced-based approach to the evaluation of patients with a clinical suspicion of deep vein thrombosis (DVT).

Deep Vein Thrombosis (DVT): Treatment

Venous Thromboembolism

To provide an evidence-based approach to treatment of patients presenting with deep vein thrombosis (DVT).

Heparin-Induced Thrombocytopenia (HIT)

Anticoagulant & Antiplatelet Drugs, Ischemic Vascular Diseases, Venous Thromboembolism

To assist clinicians with the diagnosis and initial management of heparin-induced thrombocytopenia (HIT) and suspected HIT.

Références TEV



Pregnancy: Venous Thromboembolism Treatment



Pregnancy & Thrombosis, Venous Thromboembolism

To provide an evidence-based approach to treatment of deep vein thrombosis and/or pulmonary embolism during pregnancy and the postpartum period.

Apixaban (Eliquis®)

Anticoagulant & Antiplatelet Drugs, Atrial Fibrillation, Novel Oral Anticoagulants, 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).

Dabigatran (Pradaxa®)

Anticoagulant & Antiplatelet Drugs, Atrial Fibrillation, Novel Oral Anticoagulants, Venous Thromboembolism

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

Deep Vein Thrombosis (DVT): Diagnosis

Venous Thromboembolism

To provide an evidenced-based approach to the evaluation of patients with a clinical suspicion of deep vein thrombosis (DVT).

Deep Vein Thrombosis (DVT): Treatment

Venous Thromboembolism

To provide an evidence-based approach to treatment of patients presenting with deep vein thrombosis (DVT).

Heparin-Induced Thrombocytopenia (HIT)

Anticoagulant & Antiplatelet Drugs, Ischemic Vascular Diseases, Venous Thromboembolism

To assist clinicians with the diagnosis and initial management of heparin-induced thrombocytopenia (HIT) and suspected HIT.

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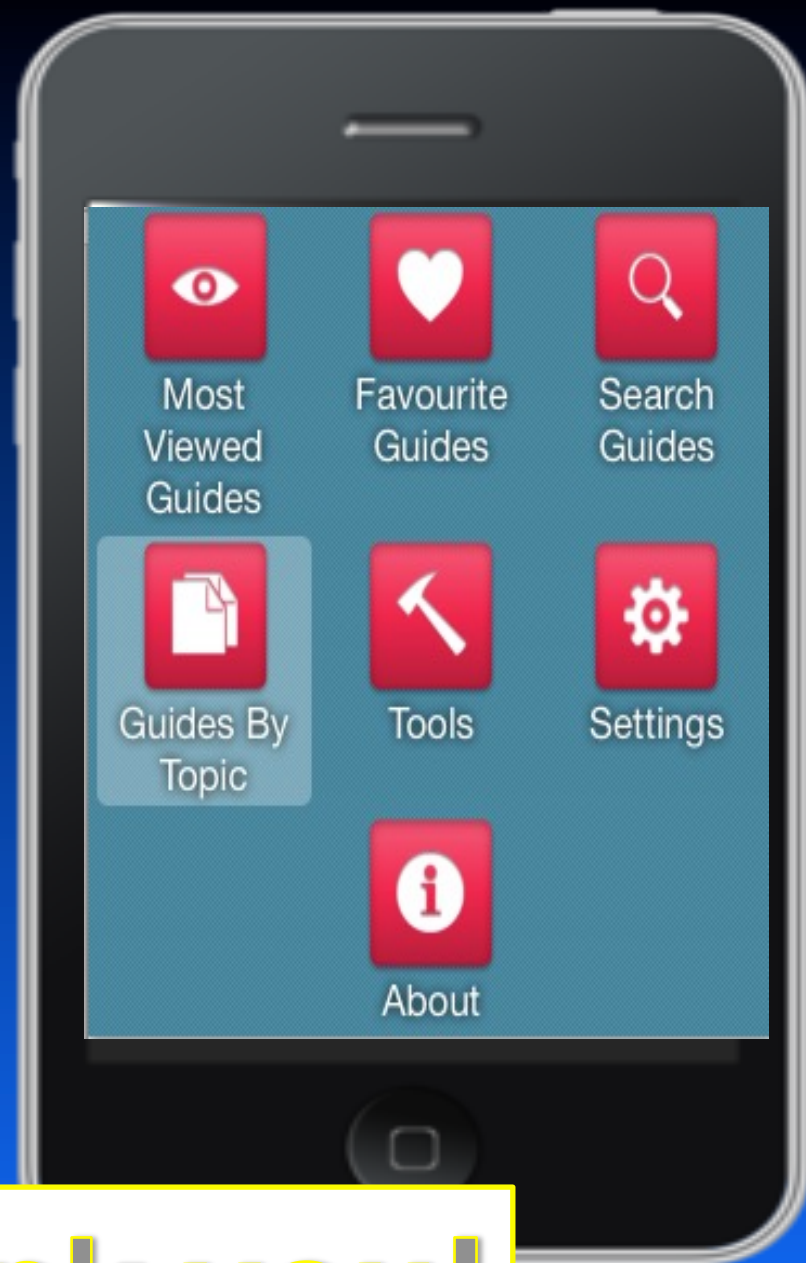
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References: "App"

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Merci, Thank you!