



# Prévention des Thromboses veineuses au cours des Cancers digestifs

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Pour le Groupe Francophone Thrombose et Cancer -International Initiative on Thrombosis and Cancer (ITAC-GFTC)

ITAC<sup>CME</sup>GFTC

# Association Thrombose & Cancer

1865, Armand Trousseau (Hôtel-Dieu, Paris)



## CANCER

- 4-20% des patients atteints de cancer développeront un épisode de MTEV
- 50% des patients atteints d'un cancer: présence de MTEV à l'autopsie



## MALADIE THROMBOEMBOLIQUE VEINEUSE

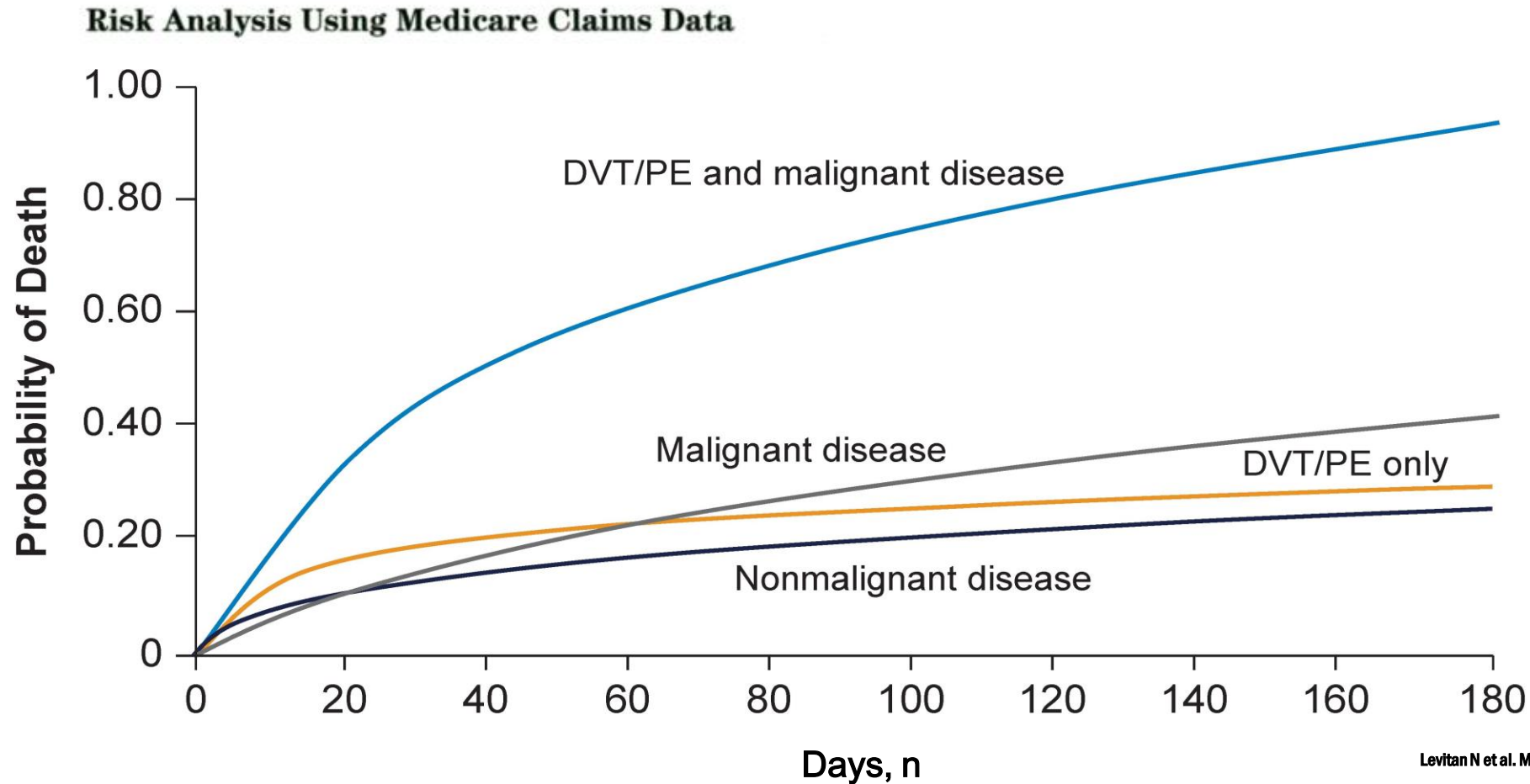
- 20% des patients avec MTEV ont un cancer actif
- 4-12% des patients atteints d'une MTEV idiopathique ont un cancer sous-jacent

Courtesy of Pr. Dominique Farge

1. Trousseau A. Clinique médicale de l'Hôtel-Dieu de Paris, T3:1865;654-712.
2. Farge et al. *Thromb Res*2010;125:S108-S116.
3. Falanga & Zacharski. *Ann Oncol*2005;16:696-701.
4. Monreal et al. *J Thromb Haemost*2006;4:1950-1956.

# Thrombose, 2<sup>ème</sup> Cause de Mortalité au Cours du cancer

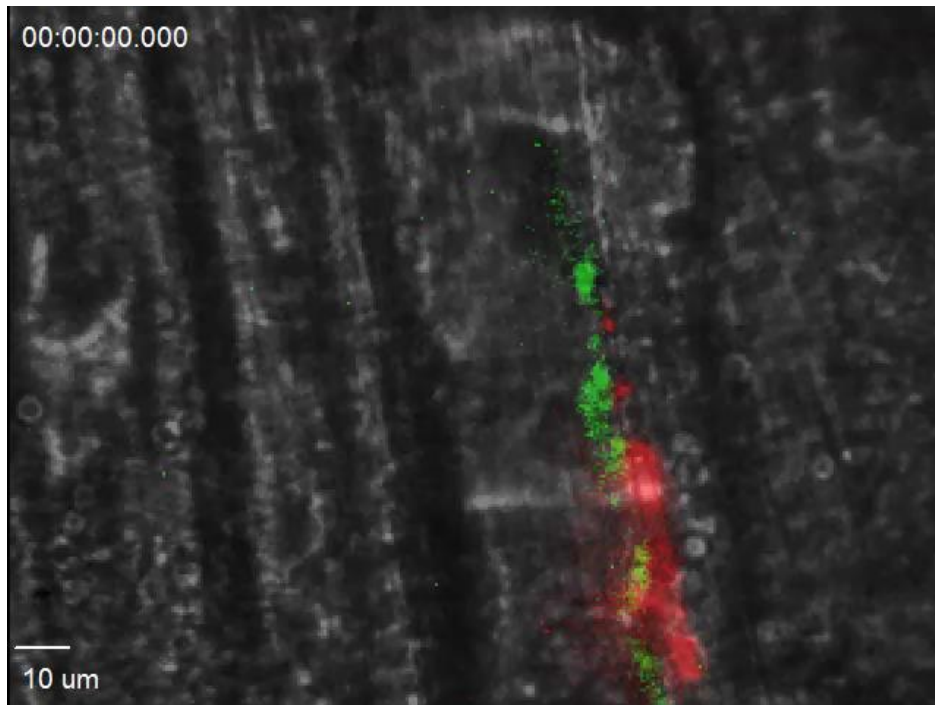
## Rates of Initial and Recurrent Thromboembolic Disease Among Patients with Malignancy Versus Those without Malignancy



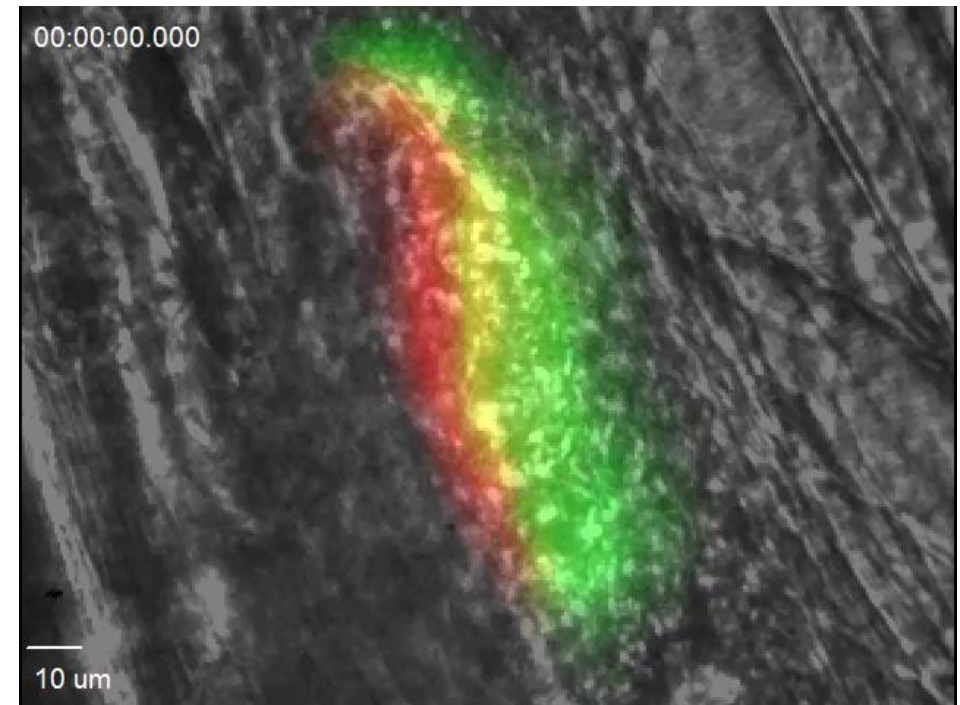
Levitan N et al. Medicine (Baltimore). 1999;78:285-291

# Le Cancer est associé à un phénotype prothrombotique

Modèle murin WT



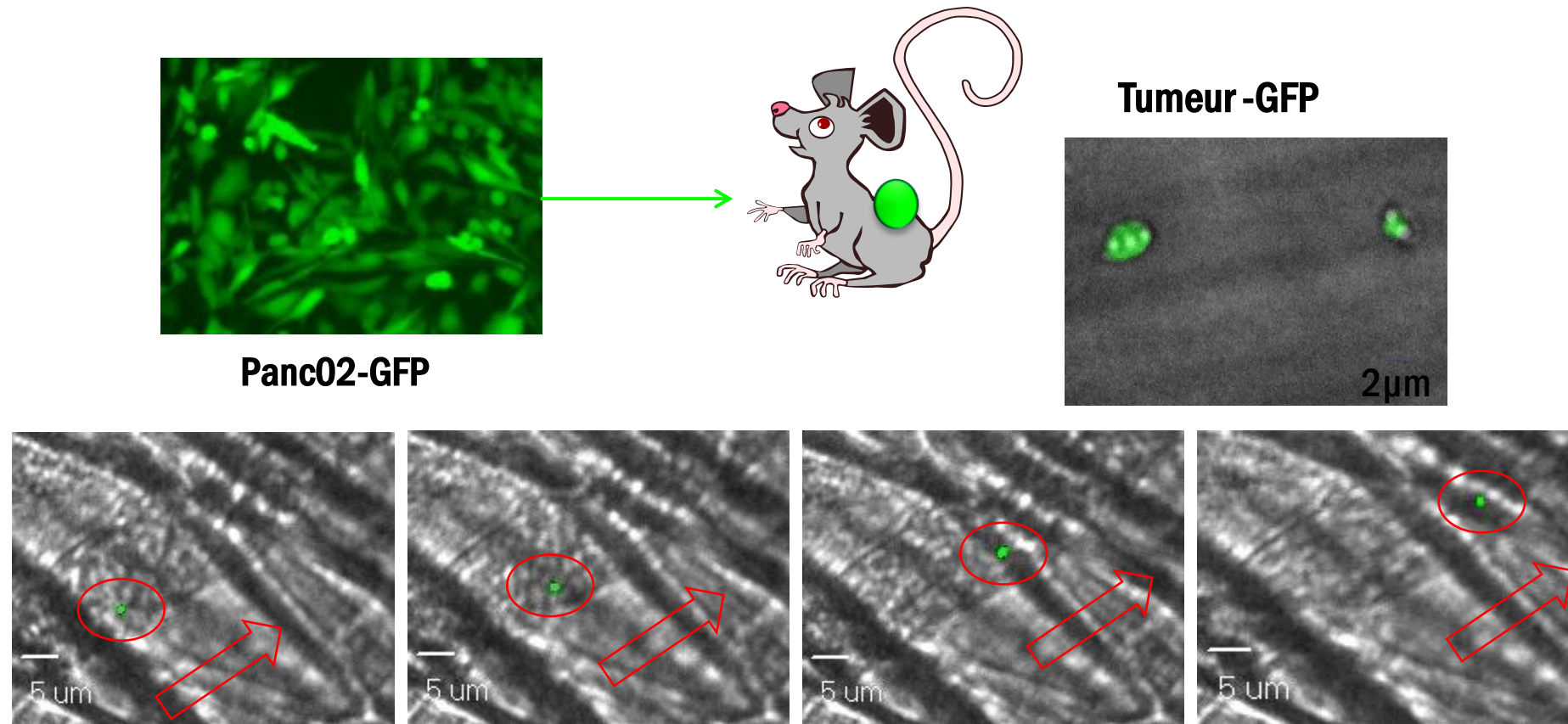
Modèle murin ectopique de cancer du pancreas



Panc02

Courtesy Soray Mezouar

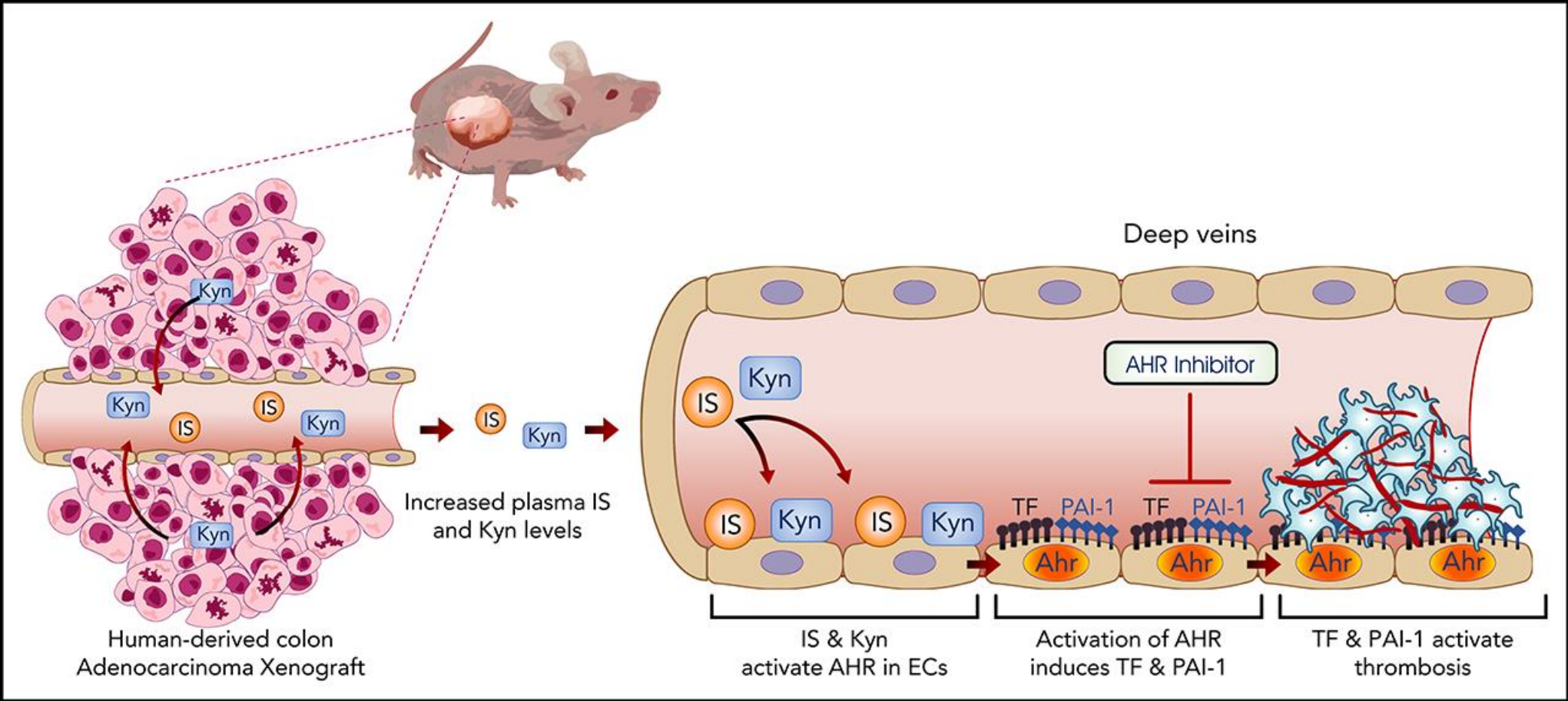
# Le Cancer est associé à un phénotype prothrombotique



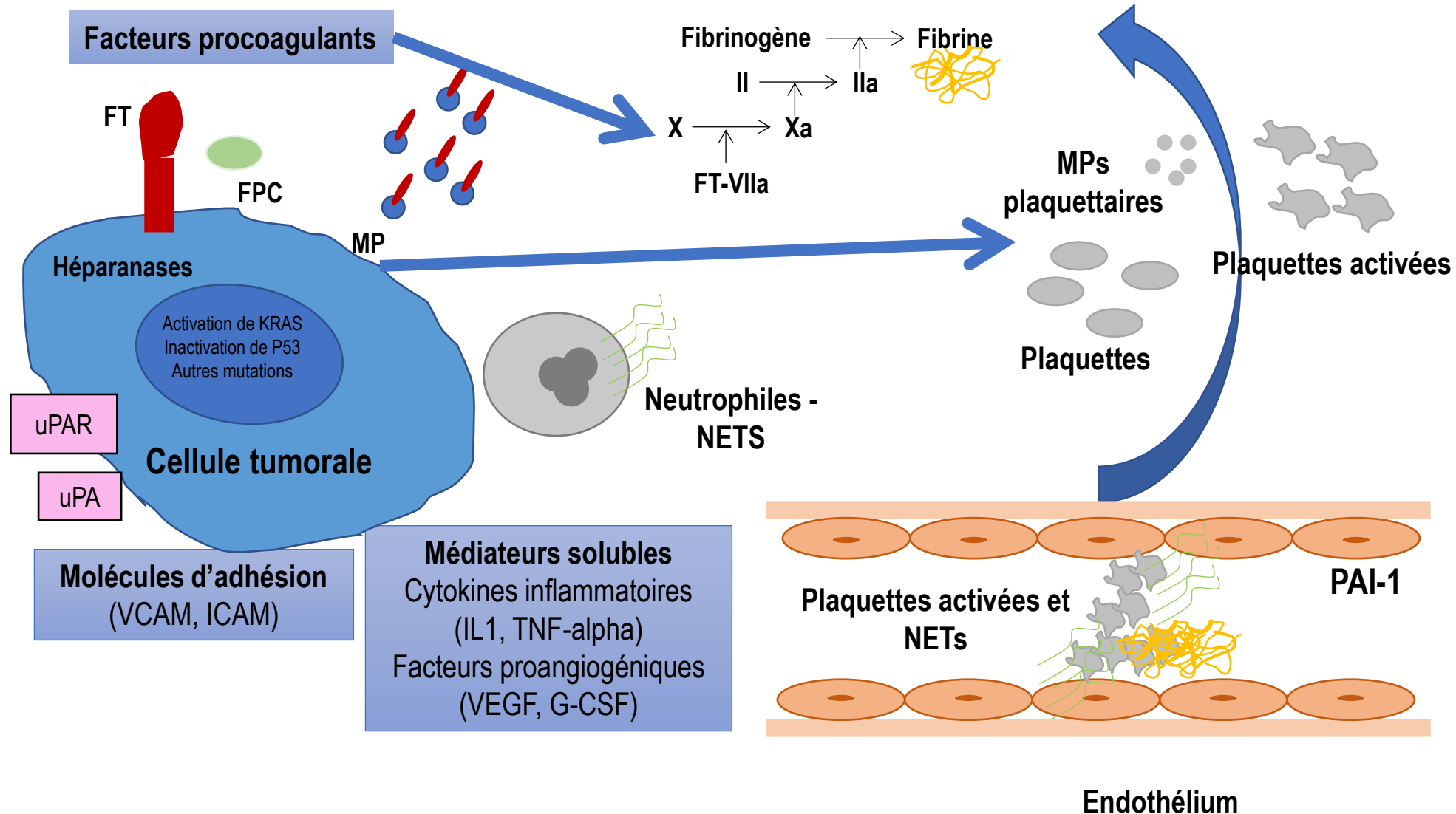
**La tumeur libère des vésicules de taille correspondant à celle des microparticules dans la circulation sanguine**



# METABOLITES IN A MOUSE CANCER MODEL ENHANCE VENOUS THROMBOGENICITY THROUGH THE ARYL HYDROCARBON RECEPTOR-TISSUE FACTOR AXIS

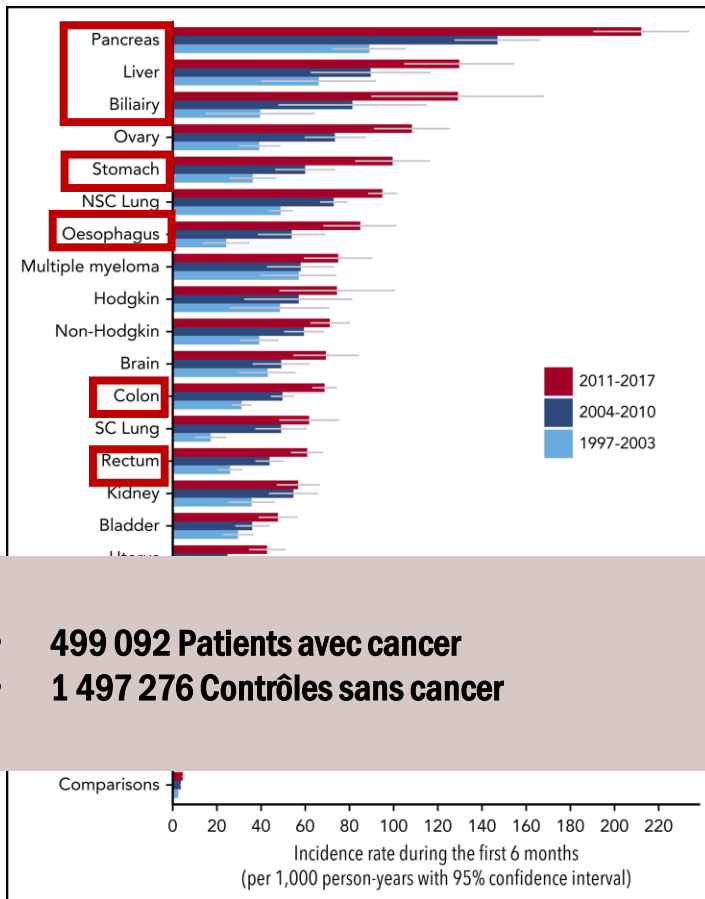


# Le Cancer est associé à un phénotype prothrombotique



# Le Risque de MTEV dépend du Type de Cancer

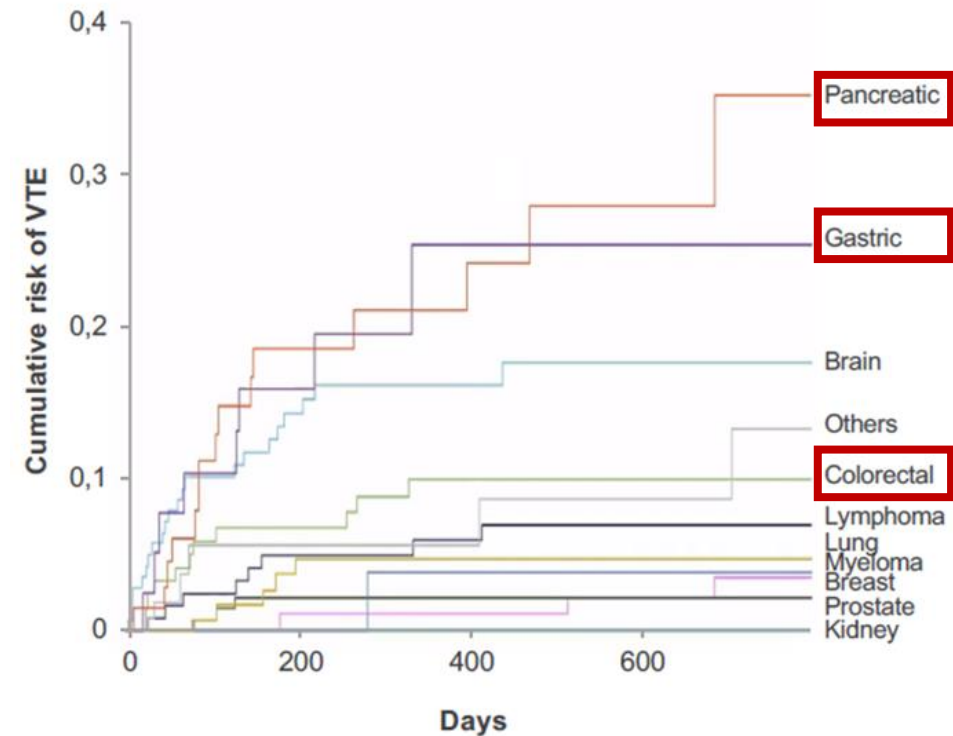
## Etude de population (1997-2017)



- 499 092 Patients avec cancer
- 1 497 276 Contrôles sans cancer

Mudler et al. Blood. 2021;137(14):1959-1969.

## Etude prospective Vienna CAT Study (n=1409)





# Incidence de la MTEV après Chirurgie Oncologique Majeure

## Nationwide Inpatient Sample (NIS)

n=2,508,916

Table 3. Multivariable Logistic Regression Analysis After Fitting With the Generalized Estimating Equation and Covariables for Predicting Mortality in the Context of VTE Following Major Cancer Surgery, Nationwide Inpatient Sample, January 1, 1999, Through December 30, 2009<sup>a</sup>

Cancer Type	Mortality			OR (95% CI)	P Value
	Overall, %	Without VTE, %	With VTE, %		
Overall	2.0	1.9	12.0	5.30 (4.88-5.76)	<.001
Colectomy	3.1	2.9	11.3	3.74 (3.34-4.19)	<.001
Cystectomy	2.5	2.3	9.6	4.58 (3.22-6.51)	<.001
Esophagectomy	7.2	6.9	13.6	2.01 (1.13-3.56)	.02
Gastrectomy	5.7	5.5	14.7	2.81 (2.12-3.73)	<.001
Hysterectomy	0.4	0.3	5.2	10.93 (6.85-17.45)	<.001
Lung resection	2.9	2.6	19.8	8.73 (7.39-10.31)	<.001
Pancreatectomy	4.9	4.7	13.2	3.08 (2.05-4.61)	<.001
Prostatectomy	0.1	0.1	3.9	56.42 (30.54-104.25)	<.001

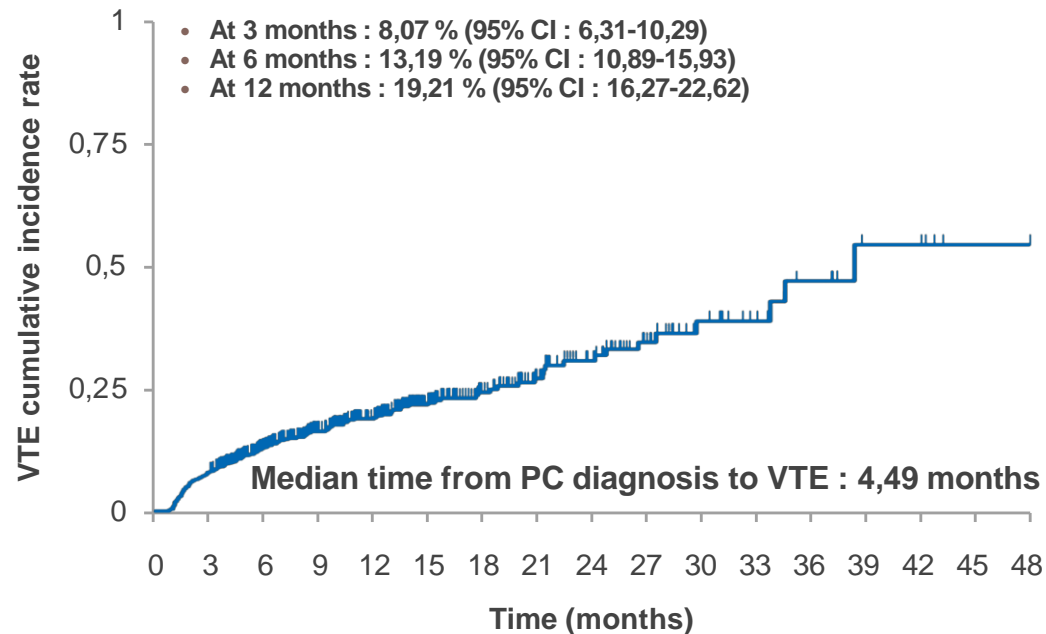
Abbreviations: OR, odds ratio; VTE, venous thromboembolism.

<sup>a</sup> Covariables include age, sex, race, Charlson comorbidity index, insurance status, median household income by zip code, annual hospital volume, hospital location, hospital region, and hospital teaching status.

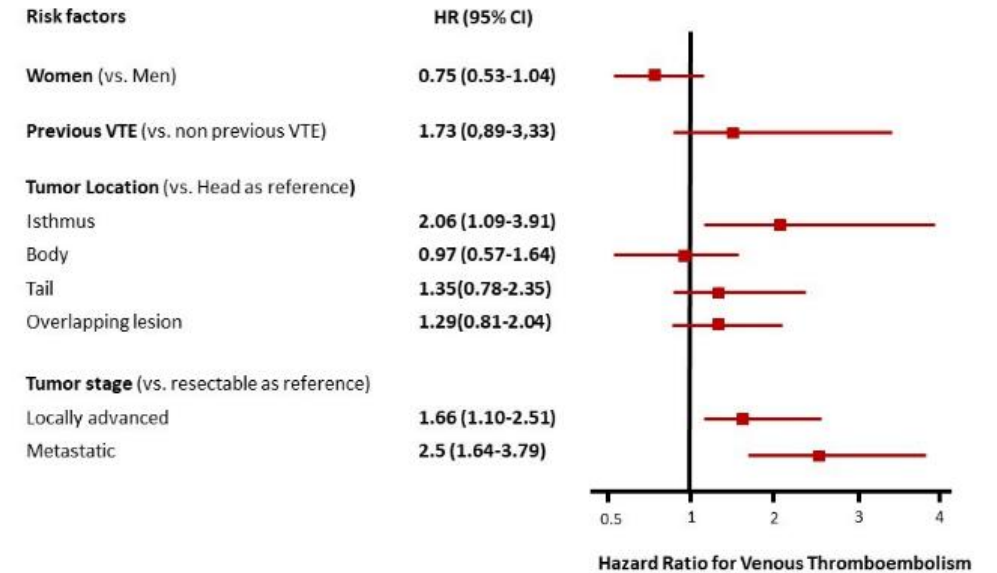
# Adénocarcinome du pancréas : BACAP-VTE STUDY

## Etude française, observationnelle, prospective, multicentrique

- Population : 731 patients atteints d'un adénocarcinome du pancréas inclus (mai 2014-novembre 2018)
- Episode de MTEV chez 20,79 % des patients (54% de MTEV asymptomatiques) au cours d'une durée médiane de suivi de 19,3 mois



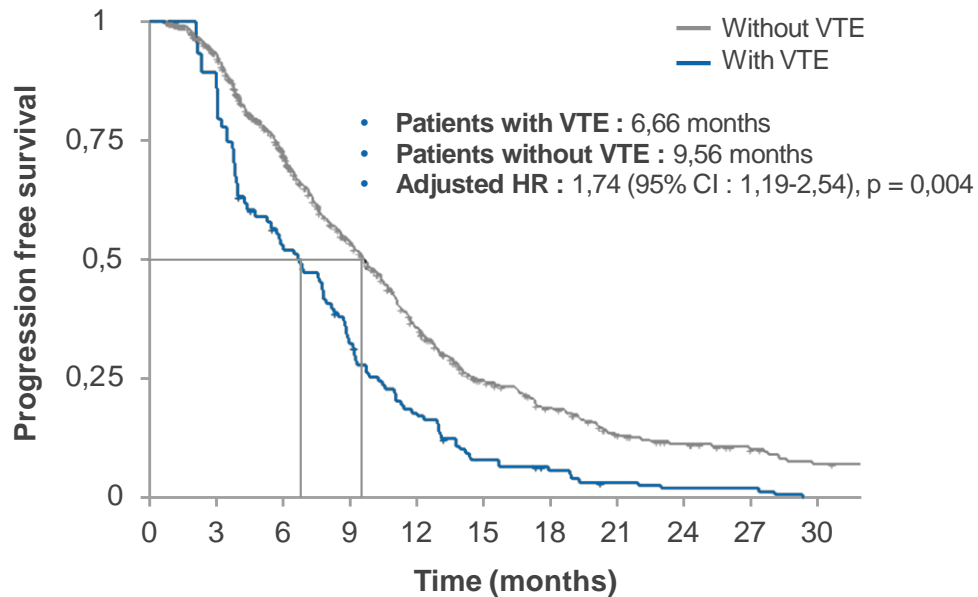
### Multivariate Analysis



Frere C, Boumet B et al. *Gastroenterology* 2020 ; 158 : 1346-1358.

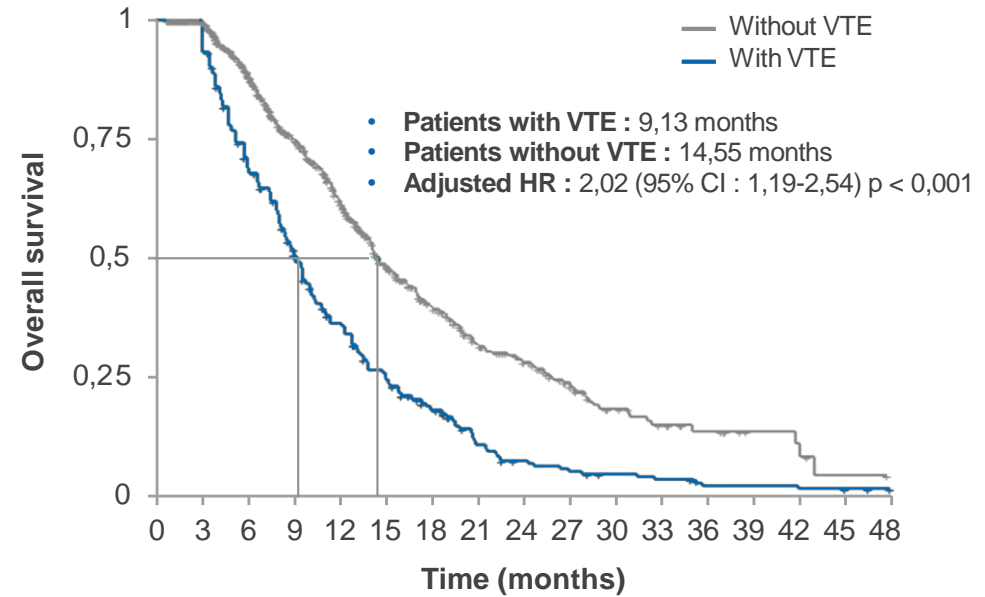
# Adénocarcinome du pancréas : BACAP-VTE STUDY

Etude française, observationnelle, prospective, multicentrique



Number at risk :

—	731	624	427	277	167	95	64	36	26	17	11
—	0	52	48	36	21	11	7	4	3	3	0



Number at risk :

—	731	672	521	379	279	175	119	80	59	38	23	16	11	5	4	1	0
—	0	59	65	57	44	37	24	13	10	10	8	6	3	4	4	3	1

→ Décès : 71 % des patients avec MTEV vs 46,92 % des patients sans MTEV  
 OR = 2,88 ; IC<sub>95</sub> : 1,96-4,21; p < 0,0001

# Recommandations internationales ITAC 2019

## Groupe d'experts internationaux multidisciplinaire:

15 experts, 2 méthodologistes, 1 infirmière, 2 patients, 83 reviewers indépendants

## Méthodologie GRADE

Avec le soutien de



Adoptées par



Review

## 2019 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer



*Dominique Farge\*, Corinne Frere\*, Jean M Connors, Cihan Ay, Alok A Khorana, Andres Munoz, Benjamin Brenner, Ajay Kakkar, Hanadi Rafii, Susan Solymoss, Dialina Brilhante, Manuel Monreal, Henri Bounameaux, Ingrid Pabinger, James Douketis, and the International Initiative on Thrombosis and Cancer (ITAC) advisory panel*

Venous thromboembolism (VTE) is the second leading cause of death in patients with cancer. These patients are at a high risk of VTE recurrence and bleeding during anticoagulant therapy. The International Initiative on Thrombosis and Cancer is an independent academic working group aimed at establishing a global consensus for the treatment and prophylaxis of VTE in patients with cancer. The International Initiative on Thrombosis and Cancer last updated its evidence-based clinical practice guidelines in 2016 with a free, web-based mobile phone application, which was subsequently endorsed by the International Society on Thrombosis and Haemostasis. The 2019 International Initiative on Thrombosis and Cancer clinical practice guidelines, which are based on a systematic review of the literature published up to December, 2018, are presented along with a Grading of Recommendations Assessment Development and Evaluation scale methods, with the support of the French National Cancer Institute. These guidelines were reviewed by an expanded international advisory committee and endorsed by the International Society on Thrombosis and Haemostasis. Results from head-to-head clinical trials that compared direct oral anticoagulant with low-molecular-weight heparin are also summarised, along with new evidence for the treatment and prophylaxis of VTE in patients with cancer.

*Lancet Oncol* 2019

Published Online  
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[http://dx.doi.org/10.1016/S1470-2045\(19\)30336-5](http://dx.doi.org/10.1016/S1470-2045(19)30336-5)

\*Contributed equally

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THE LANCET  
Oncology



Farge D, Frere C, et al. *Lancet Oncol*. 2019 Oct;20(10):e566-e581

# Prévention de la MTEV en chirurgie

Extended thromboprophylaxis following major abdominal/pelvic cancer-related surgery: A systematic review and meta-analysis of the literature

4 RCTs, 14 observational studies n=7795 cancer patients

## VTE

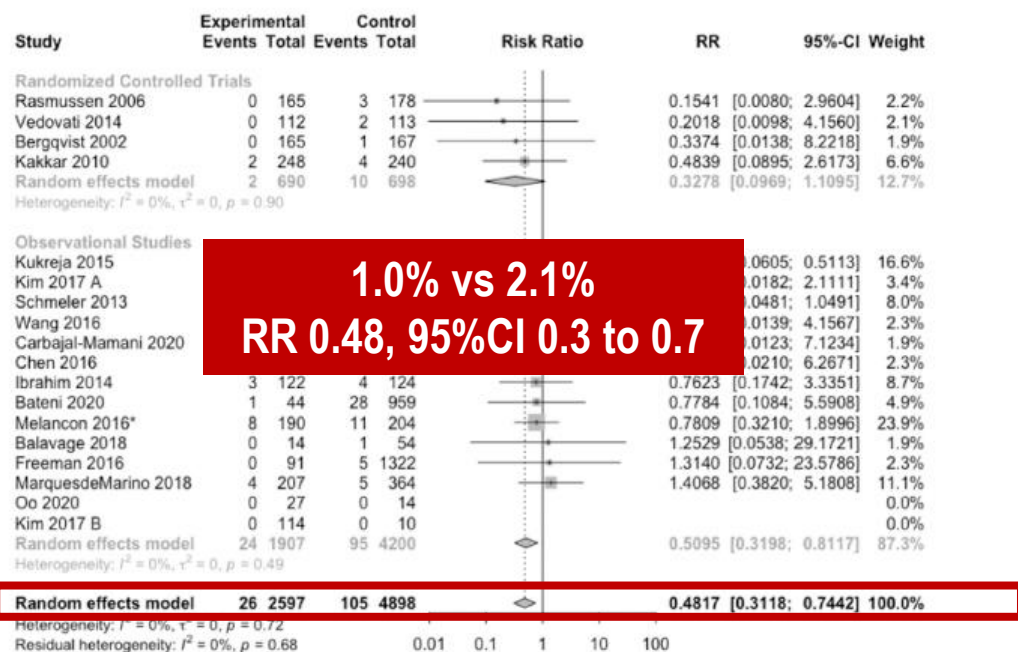


Fig. 4. Comparison of 30-day clinical VTE incidence with (experimental) versus without (control) extended duration thromboprophylaxis. Results presented as pooled risk ratios, stratified by study design.

## Bleeding

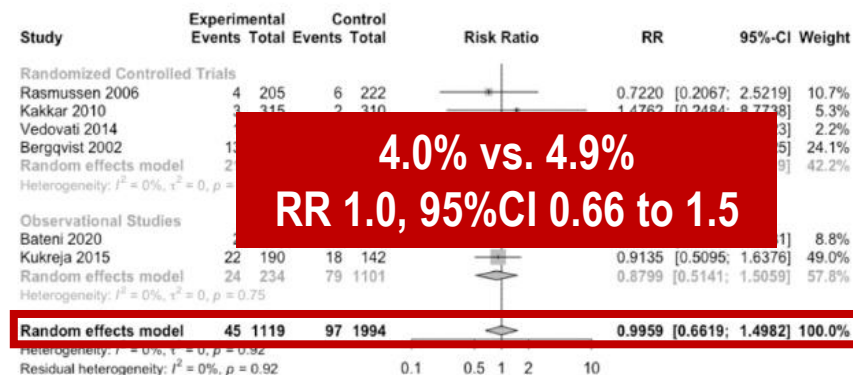
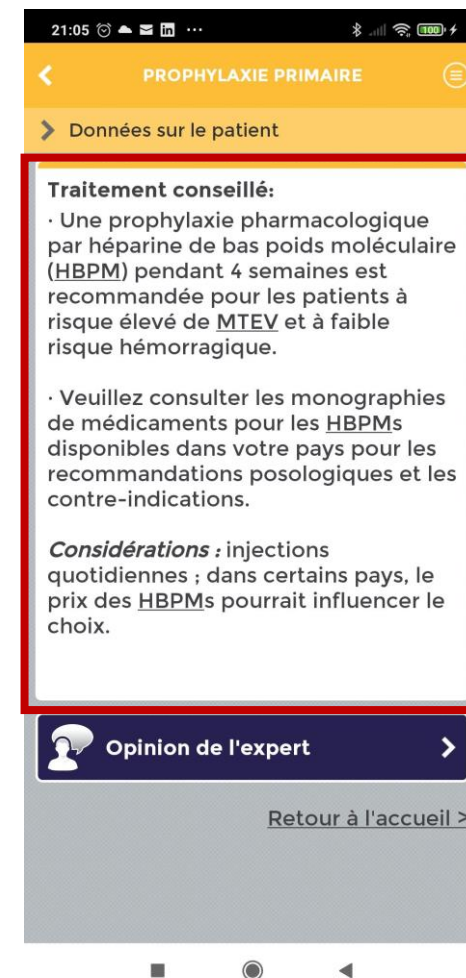
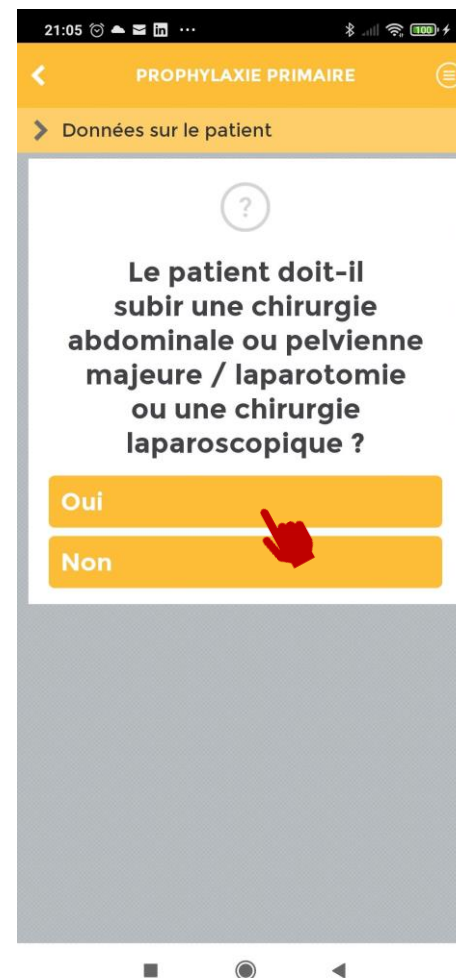
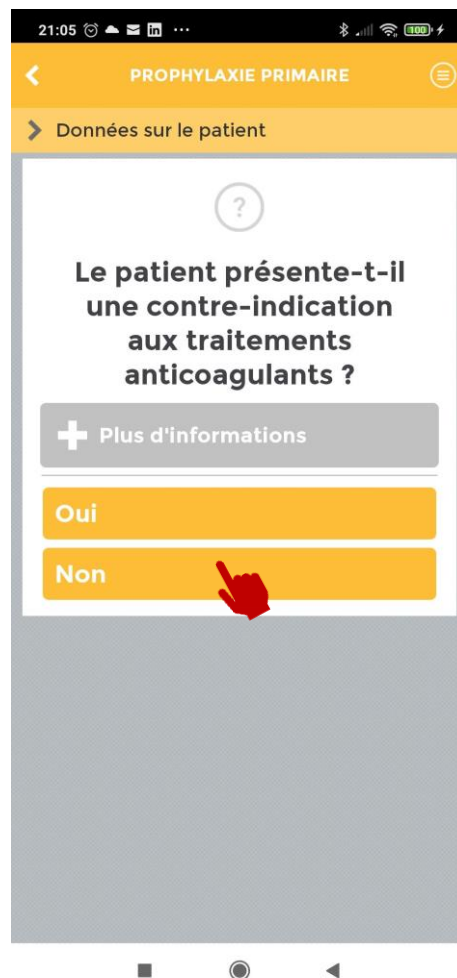
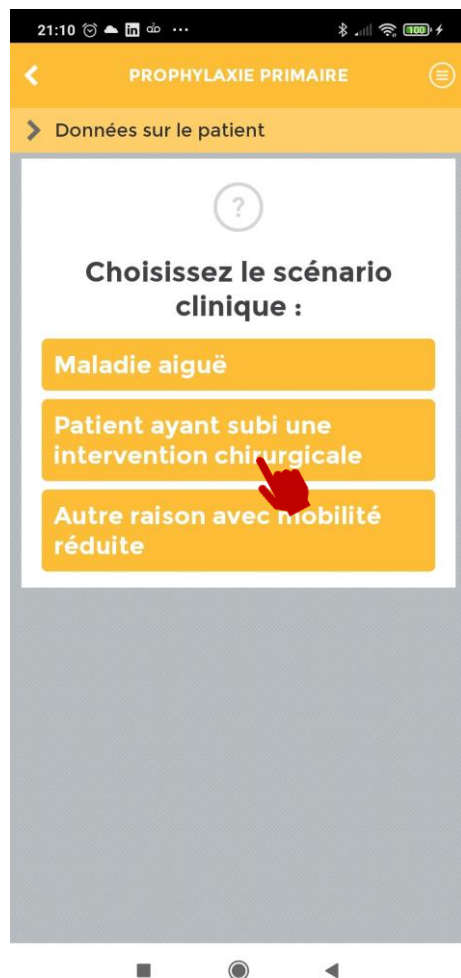
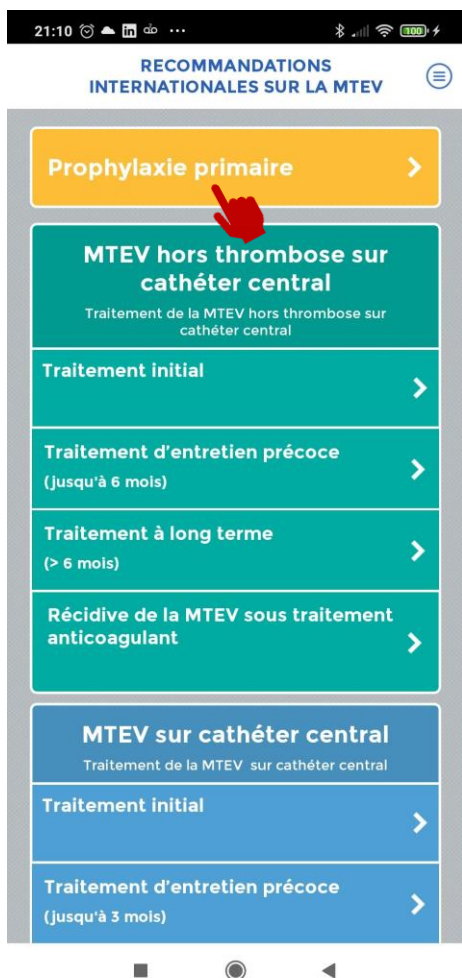


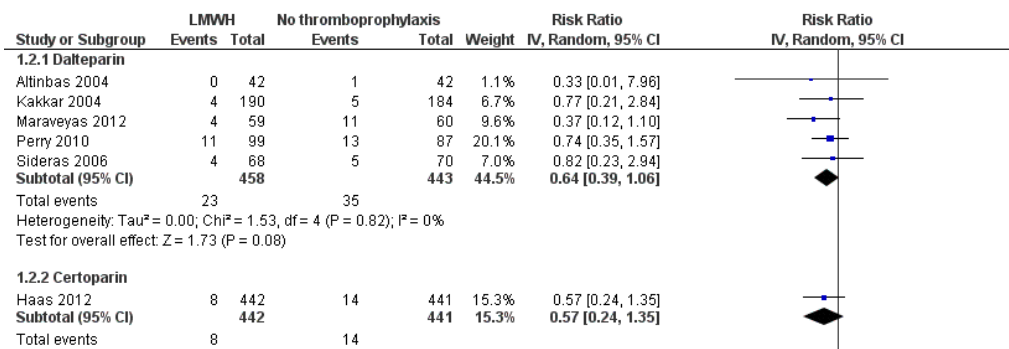
Fig. 5. Incidence of bleeding complications (major and clinically-relevant non-major bleeding) with (experimental) versus without (control) extended duration thromboprophylaxis. Results presented as pooled risk ratios, stratified by study design.



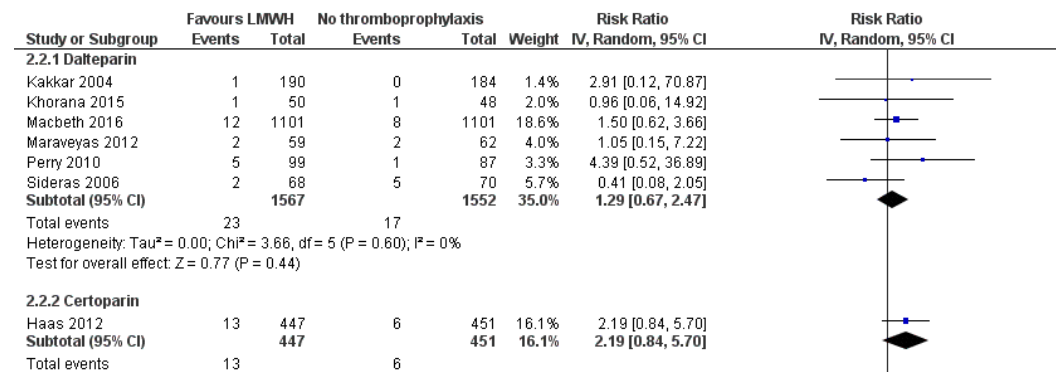
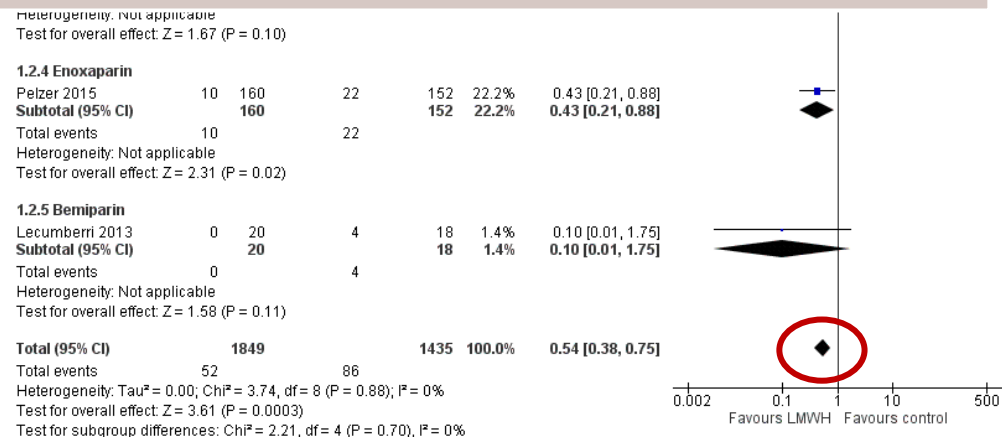
# Prévention de la MTEV en chirurgie



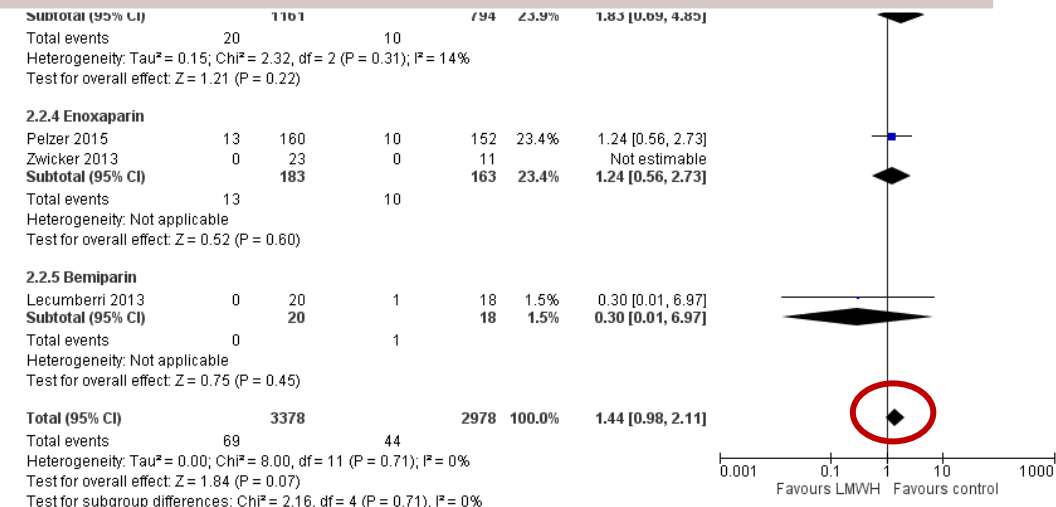
# Prévention de la MTEV chez les patients ambulatoires : HBPM



**LMWH significantly reduced symptomatic VTE :  
RR 0.54, 95% CI 0.38 to 0.75**



**No difference in major bleedings :  
RR 1.44, 95% CI 0.98 to 2.11**



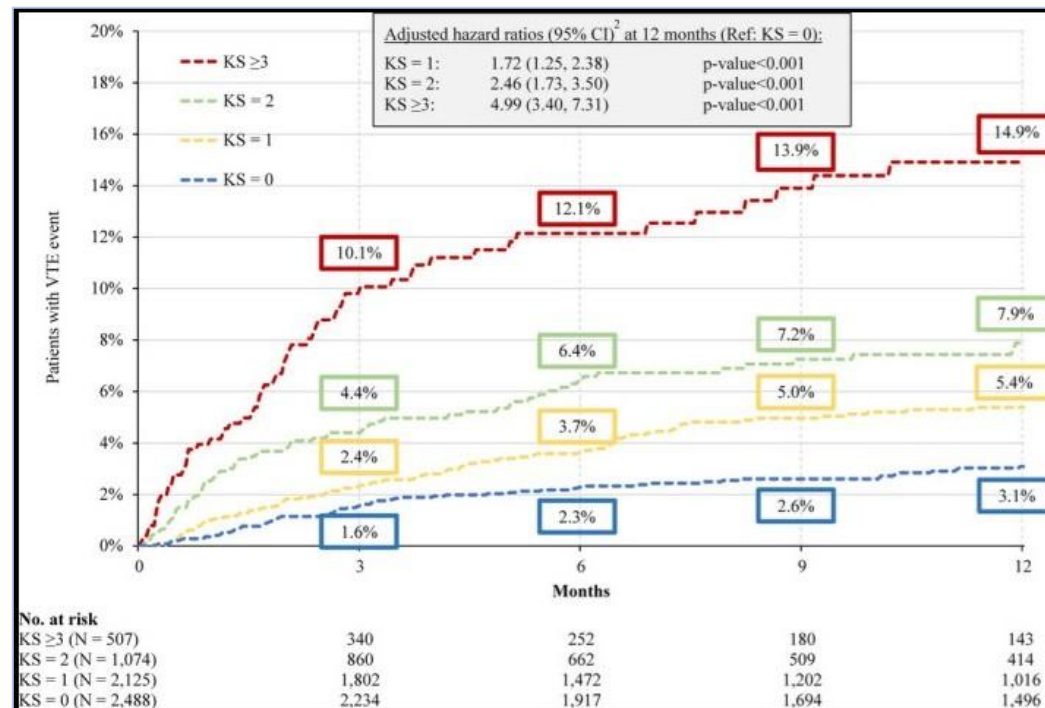
# Modèles de Stratification du Risque

## Score de Khorana

Type de cancer	
Tumeurs à très haut risque : <b>Estomac, Pancréas</b>	+2
Tumeurs à haut risque : <i>Lymphome, Poumon, Vessie, Gynécologique, Testicule</i>	+1
Plaquettes $\geq 350$ G/L	+1
Hémoglobine $< 10$ g/dL ou utilisation ASE	+1
Leucocytes $\geq 11 \times 10^9/L$	+1
IMC $\geq 35$ kg/m <sup>2</sup>	+1

Khorana AA et al. Blood. 2008;111:4902-4907

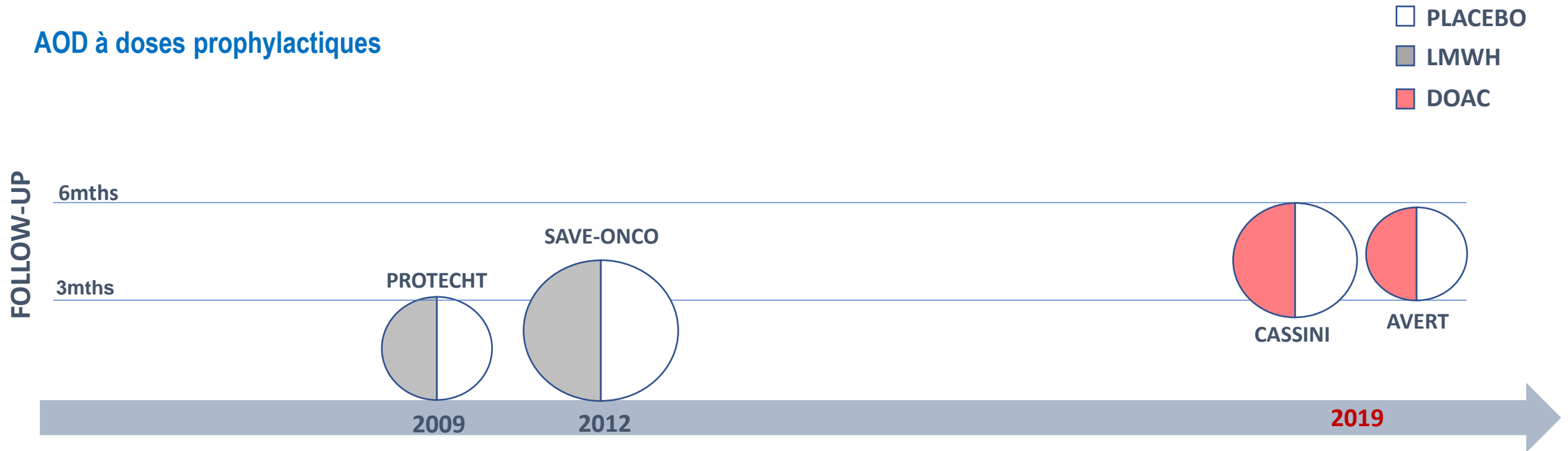
## Kaplan-Meier Rates of VTE Up to 12 Months of Follow-Up US patients with cancer, 2012-2017 (N = 6,124)



Khorana AA et al. Cancer Med. 2020;9:8062-8073

# Prévention de la MTEV chez les patients ambulatoires

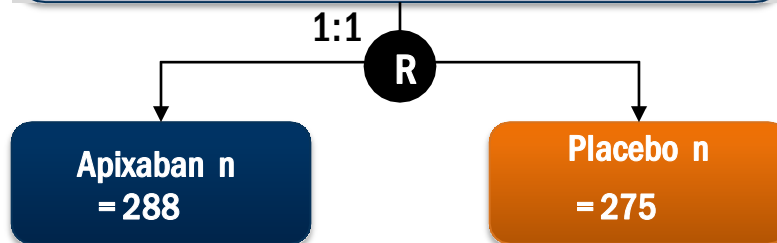
## AOD à doses prophylactiques



# Etudes Randomisées contrôlées AOD *versus* Placebo

## AVERT<sup>1</sup>

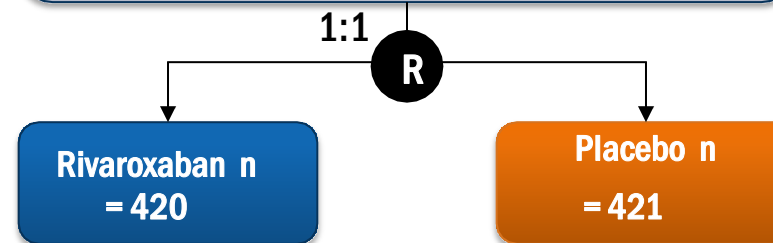
Newly diagnosed with cancer after remission (partial or complete) and initiating new course of chemotherapy x 3 months with Khorana score  $\geq 2$



- Efficacy outcome: proximal DVT/PE, symptomatic distal lower-upper extremity DVT, VTE-related death
- Safety outcome: ISTH major bleeding

## CASSINI<sup>2</sup>

Ambulatory outpatients with solid tumor or lymphoma<sup>a</sup>, Khorana score  $\geq 2$ , expected survival  $>6$  months, starting new systemic regimen within 1 week



- Efficacy outcome: proximal upper or lower extremity DVT/PE<sup>b</sup>, VTE-related death
- Safety outcome: ISTH major bleeding

<sup>a</sup> Including myeloma and brain tumor.

<sup>b</sup> Symptomatic or asymptomatic.

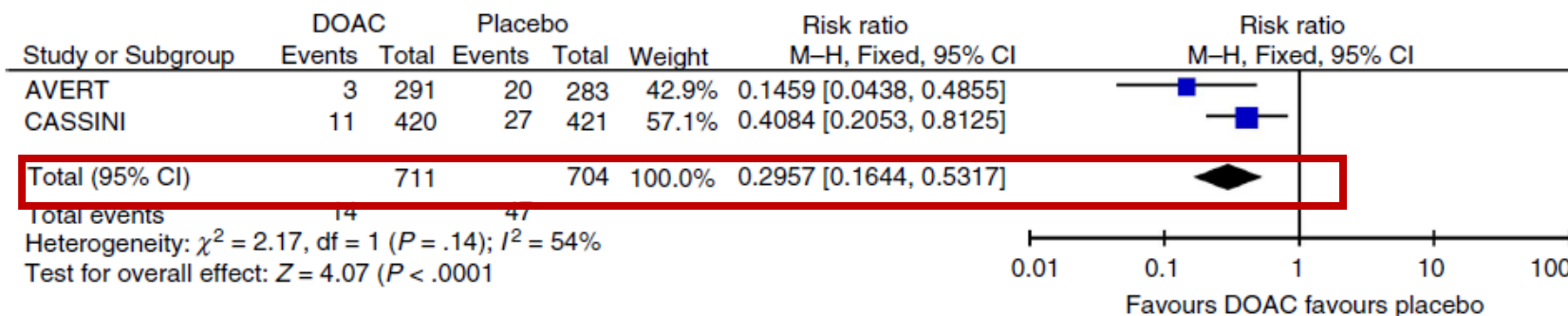
1. Carrier M et al. N Engl J Med. 2019;380:711-719.  
2. Khorana AA et al. N Engl J Med. 2019;380:720-728



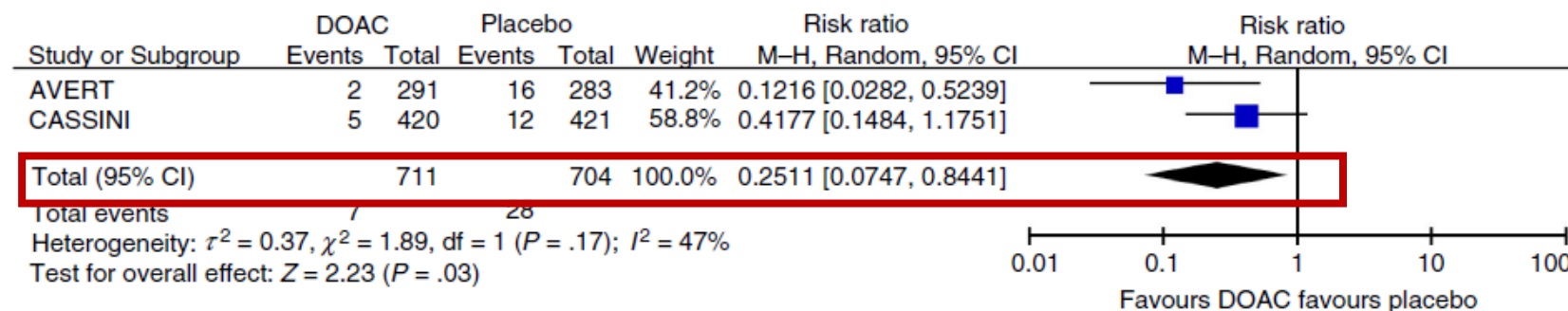
# Etudes Randomisées contrôlées AOD *versus* Placebo

## Efficacité

A Risk ratio for overall VTE (during on-treatment period: sensitivity analysis)



B Risk ratio for symptomatic VTE (during on-treatment period: sensitivity analysis)



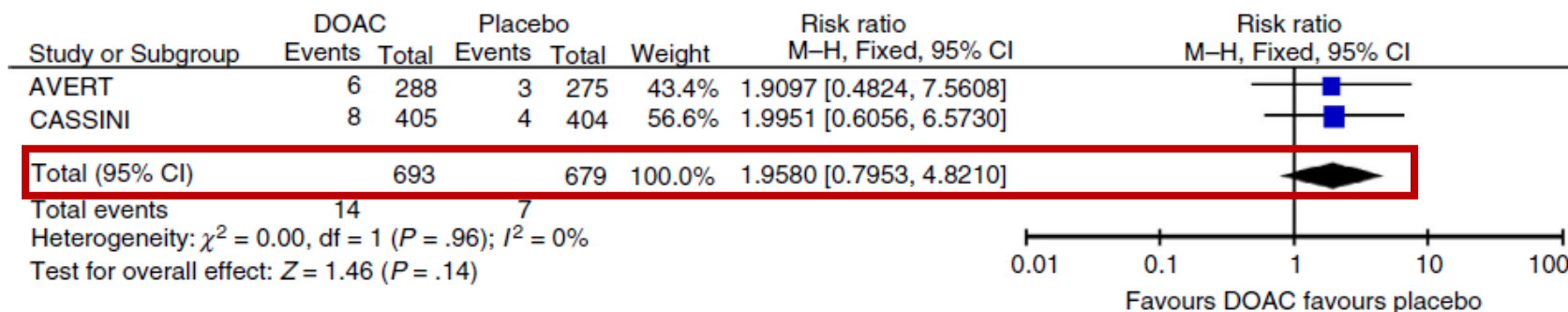
1. Carrier M et al. N Engl J Med. 2019;380:711-719.

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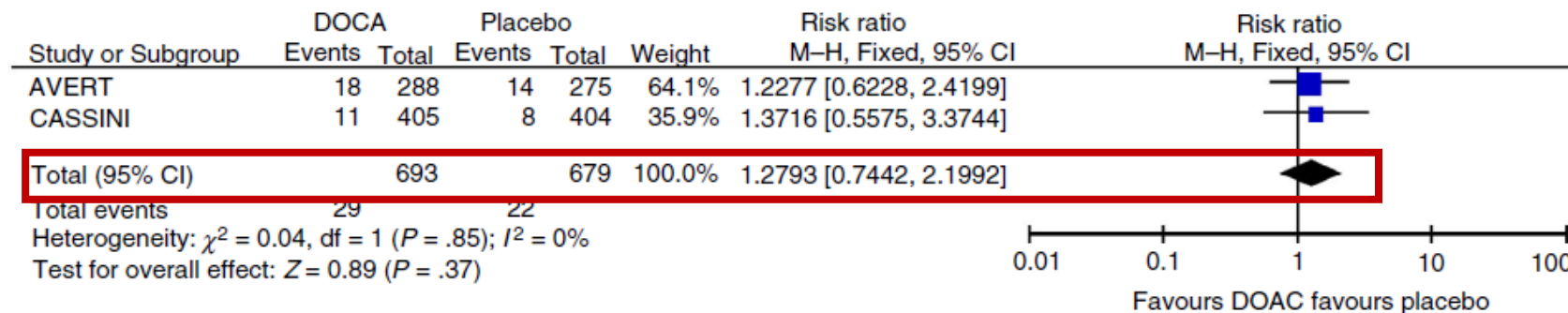
# Etudes Randomisées contrôlées AOD *versus* Placebo

## Sécurité

### A Risk ratio for major bleeding (during on-treatment period)



### B Risk ratio for clinically relevant non-major bleeding (during on-treatment period)



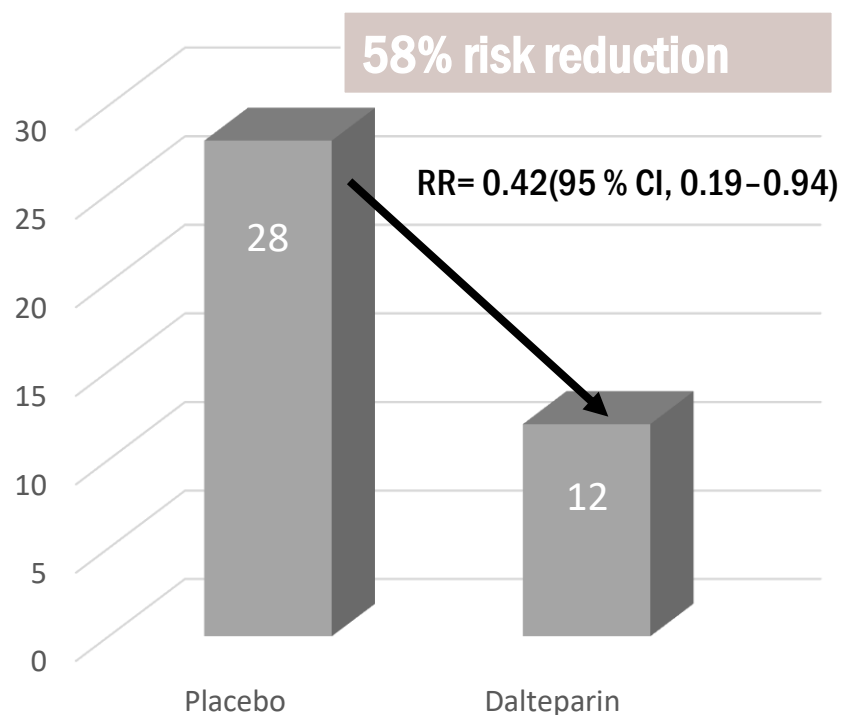
1. Carrier M et al. N Engl J Med. 2019;380:711-719.  
2. Khorana AA et al. N Engl J Med. 2019;380:720-728

# Prévention de la MTEV - Cancer du Pancréas

## FRAGEM-UK study

(n=123)

VTE rates at 12 months

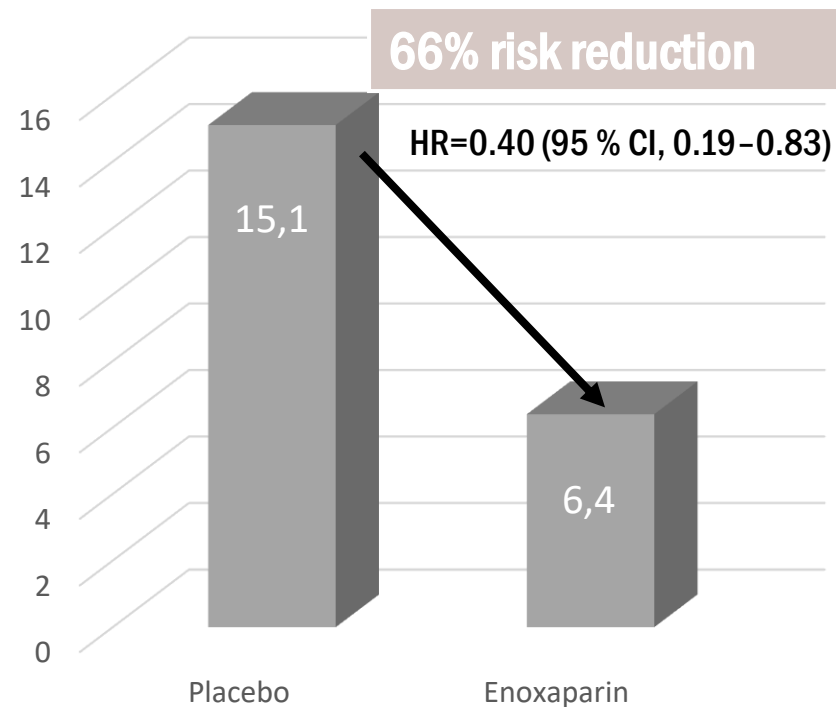


Maraveyas A et al. Eur J Cancer 2012; 48: 1283-1292.

## CONKO-004 study

(n=312)

VTE rates at 12 months

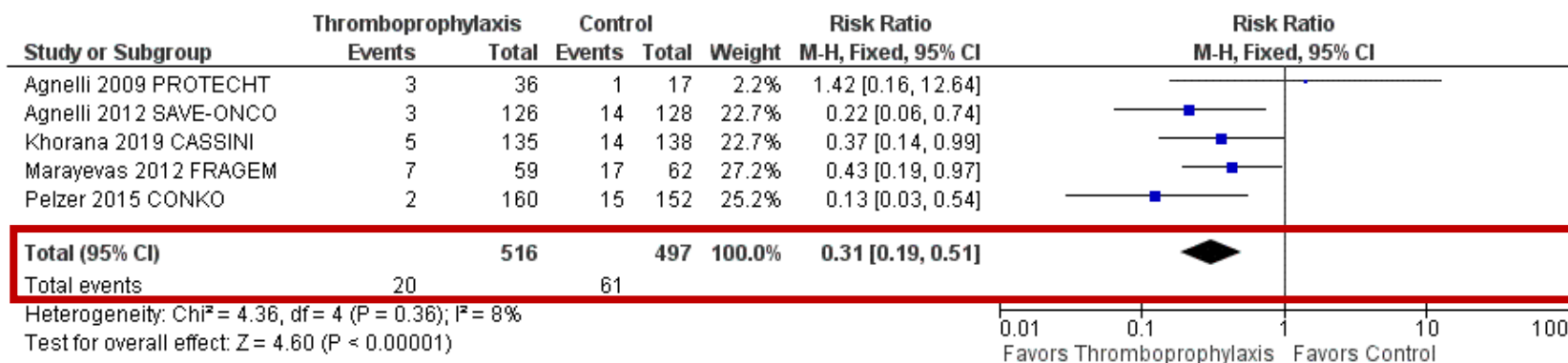


Pelzer U et al. J Clin Oncol 2015; 33: 2028-2034.

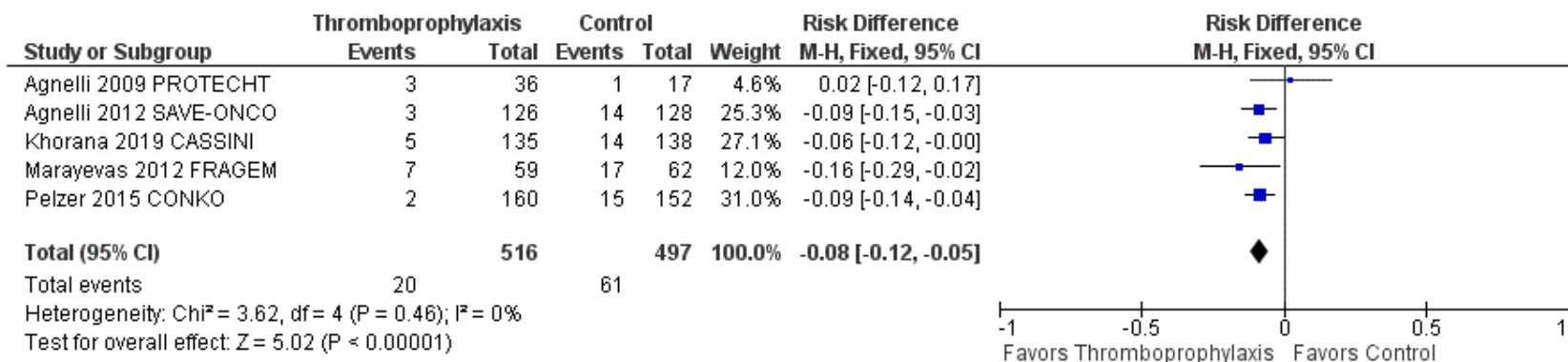
# Prévention de la MTEV - Cancer du Pancréas

## Efficacy analysis: forest plots of risk ratios (A) and risk differences (B) for venous thromboembolism

### A. Risk ratio for venous thromboembolism (fixed effect)



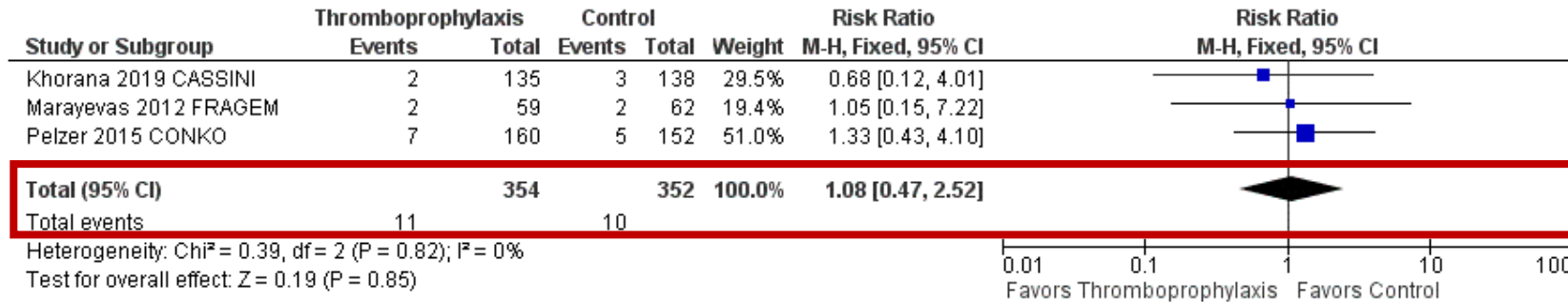
### B. Risk difference for venous thromboembolism (fixed effect)



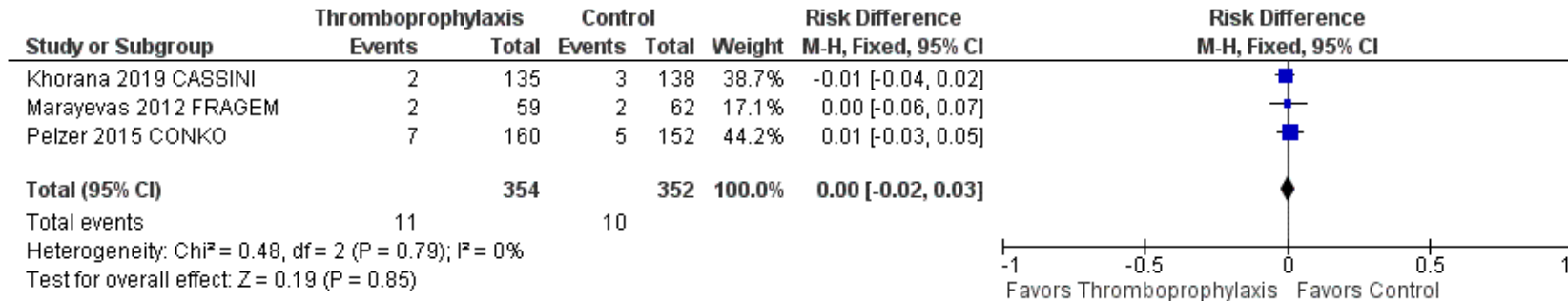
# Prévention de la MTEV - Cancer du Pancréas

## Safety analysis: forest plots of risk ratios (A) and risk differences (B) for major bleeding

### A. Risk ratio for major bleeding (fixed effect)







### B. Risk difference for major bleeding (fixed effect)

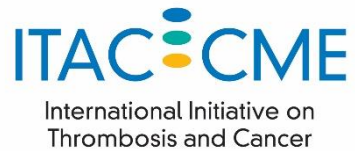




# Prévention de la MTEV - Cancer du Pancréas

## Primary Thromboprophylaxis in Pancreatic Cancer Patients: Why Clinical Practice Guidelines Should Be Implemented

Dominique Farge<sup>1,2,3,\*</sup>, Barbara Boumet<sup>4,5</sup> , Thierry Conroy<sup>6</sup>, Eric Vicaut<sup>7,8</sup>, Janusz Rak<sup>9</sup>, George Zogoulous<sup>9</sup>, Jefferey Barkun<sup>9</sup>, Mehdi Ouaisi<sup>10</sup> , Louis Buscail<sup>4,5</sup>  and Corinne Frere<sup>11,12</sup> 



- **ITAC-CME:** 1) Primary prophylaxis with LMWH in ambulatory pancreatic cancer patients with locally advanced or metastatic disease having a low risk of bleeding and receiving systemic anticancer therapy [Grade 1B] ; 2) Thromboprophylaxis with apixaban or rivaroxaban in cancer outpatients at intermediate-to-high risk (KS  $\geq$  2 prior to starting chemotherapy) with a low bleeding risk and in the absence of drug-drug interactions [Grade 1B]

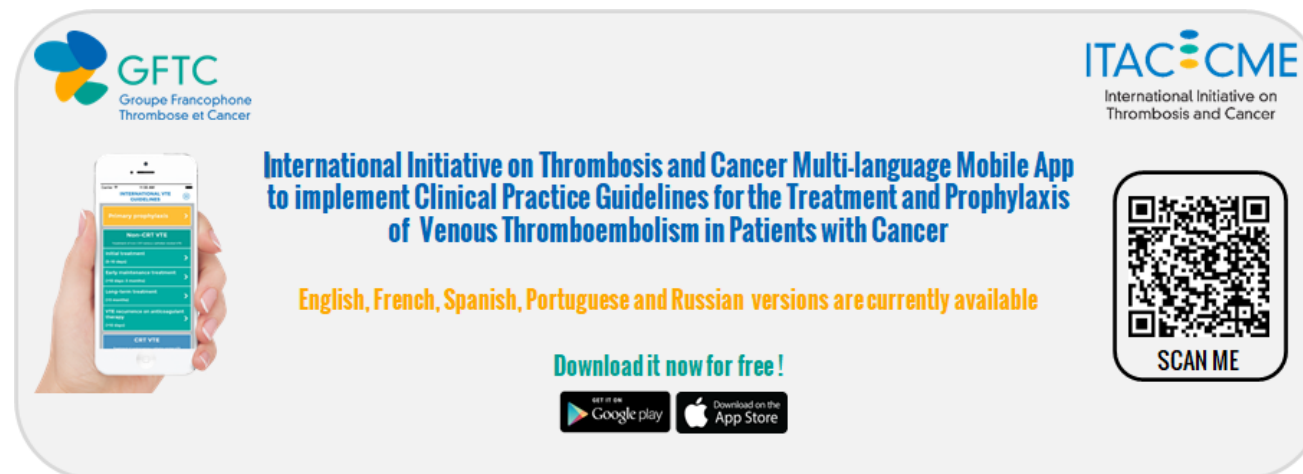


- **ASCO:** Thromboprophylaxis with apixaban, rivaroxaban or LMWH may be offered in high-risk cancer outpatients (KS  $\geq$  2 or higher prior to starting a new systemic chemotherapy regimen) in the absence of significant risk factors for bleeding and drug interactions

Farge D, Boumet B et al. *Cancers (Basel)*. 2020;12(3):618.  
Farge D, Frere C et al. *Lancet Oncol*. 2019 ;20(10):e566-e581.  
Key NS, Khorana AA et al. *J Clin Oncol*. 2020;38(5):496-520.

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The advertisement features the GFTC logo (Groupe Francophone Thrombose et Cancer) on the left and the ITAC-CME logo (International Initiative on Thrombosis and Cancer) on the right. In the center, a hand holds a smartphone displaying the app's interface. Below the phone, the text reads: "International Initiative on Thrombosis and Cancer Multi-language Mobile App to implement Clinical Practice Guidelines for the Treatment and Prophylaxis of Venous Thromboembolism in Patients with Cancer". Below this, it states: "English, French, Spanish, Portuguese and Russian versions are currently available". At the bottom center, it says "Download it now for free!" with icons for Google Play and the App Store. On the right side, there is a QR code with the text "SCAN ME" below it.