PARTICULARITES DU TRAITEMENT DE LA THROMBOSE VEINEUSE CHEZ LE PATIENT ATTEINT DE CANCER

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Journal of Thrombosis and Haemostasis, **11**: 71–80 **2013** DOI: 10.1111/jth.12071

ORIGINAL ARTICLE

International clinical practice guidelines for the treatment and prophylaxis of thrombosis associated with central venous catheters in patients with cancer

Journal of Thrombosis and Haemostasis, **11**: 56–70 **2013** DOI: 10.1111/jth.12070

ORIGINAL ARTICLE

International clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer

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J Thromb Haemost 2013; 11: 56-70

JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

2013 Recommendation	Strength of Evidence Type and Strength of Recommendation
Treatment and secondary prophylaxis	
4.1 LMWH is preferred over UFH for the initial 5 to 10 days of anticoagulation for the patient with cancer with newly diagnosed VTE who does not have severe renal impairment (defined as creatinine clearance < 30 mL/min).	Evidence: strong Recommendation type, strength: evidence based, strong
4.2 For long-term anticoagulation, LMWH for at least 6 months is preferred because of improved efficacy over VKAs. VKAs are an acceptable alternative for long-term therapy if LMWH is not available.	Evidence: strong Recommendation type, strength: evidence based, strong
4.3 Anticoagulation with LMWH or VKA beyond the initial 6 months may be considered for select patients with active cancer, such as those with metastatic disease or those receiving chemotherapy.	Evidence: insufficient Recommendation type, strength: informal consensus, weak to moderate

Lyman et al J Clin Oncol 2013; 31: 2189-2204

THROMBOSE ET CANCER : RECOMMANDATIONS

SOR 2008	CHEST 2012	ISTH 2013	ASCO 2013

Traitement Initial : HBPM/ HNF/ pentasaccharide

(<10 jours)

Traitement Long Terme : HBPM

Durée minimum 3 mois

Durée Optimale 6 mois

AMM pour cette indication :

- **Dalteparine** 200 UI/Kg par jour durant 1 mois puis 150 UI/Kg une fois par jour
- **Enoxaparine** 150 UI/Kg une fois par jour
- **Tinzaparine** 175 UI/Kg une fois par jour

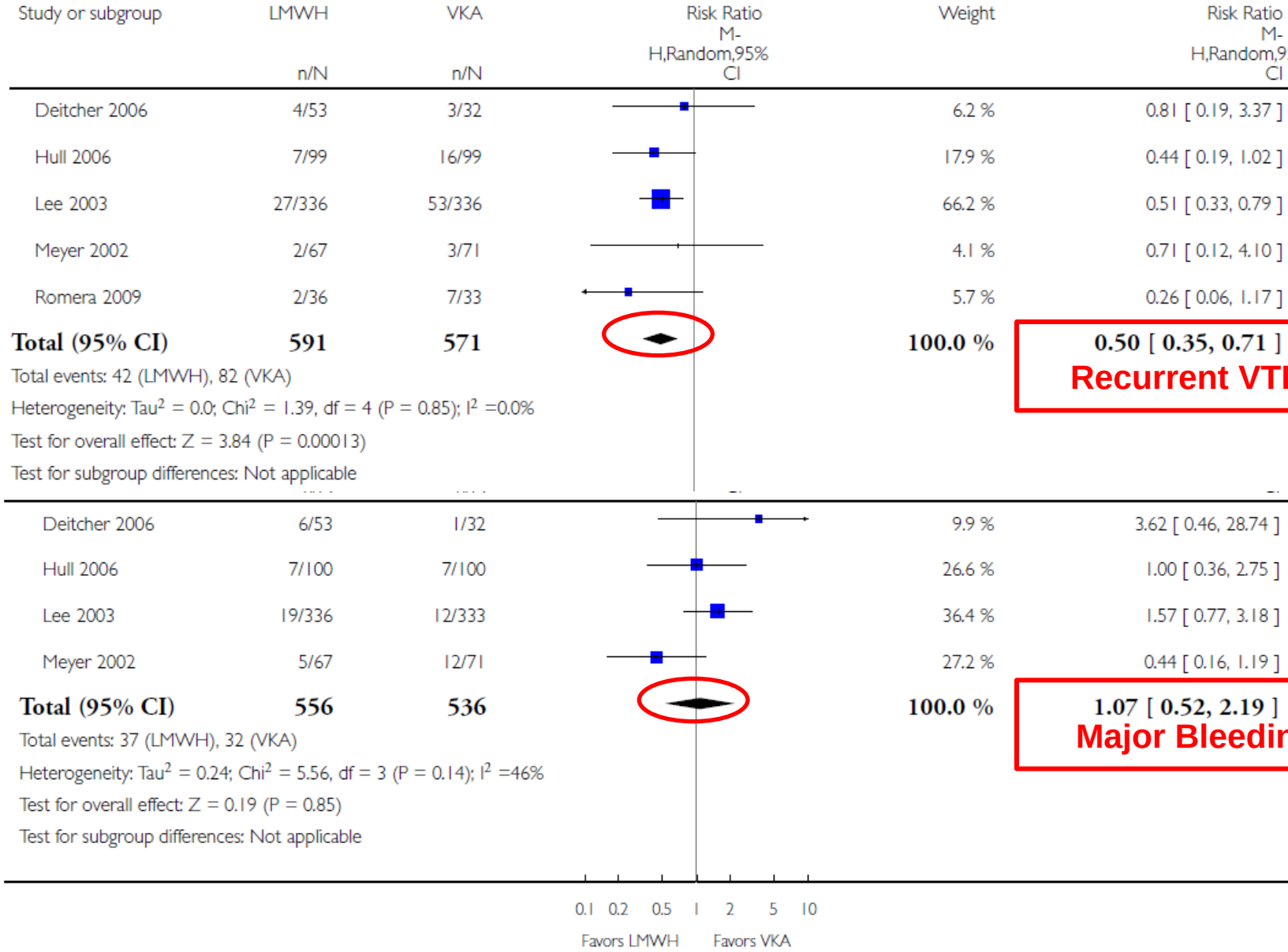
Guyatt,G et al. Chest 2012;141;48S-52S;
Farge et al J Thromb Haemost 2013; 11: 56-70;
Lyman GH et al. J Clin Oncol 2013; 31: 2189-2204

2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism

Recommendations for pulmonary embolism in cancer

Recommendations	Class[a]	Level[b]	Ref[c]
Incidental PE in patients with cancer should be managed in the same manner as symptomatic PE.	IIa	C	447–449, 463
Negative D-dimer levels have the same negative diagnostic value as in non-cancer patients.	IIa	B	98, 443
For patients with PE and cancer, weight-adjusted subcutaneous LMWH should be considered for the first 3–6 months.	IIa	B	278, 376, 377
For patients with PE and cancer, extended anticoagulation (beyond the first 3–6 months) should be considered for an indefinite period or until the cancer is cured.	IIa	C	

MEILLEURE OPTION ANTITHROMBOTIQUE?



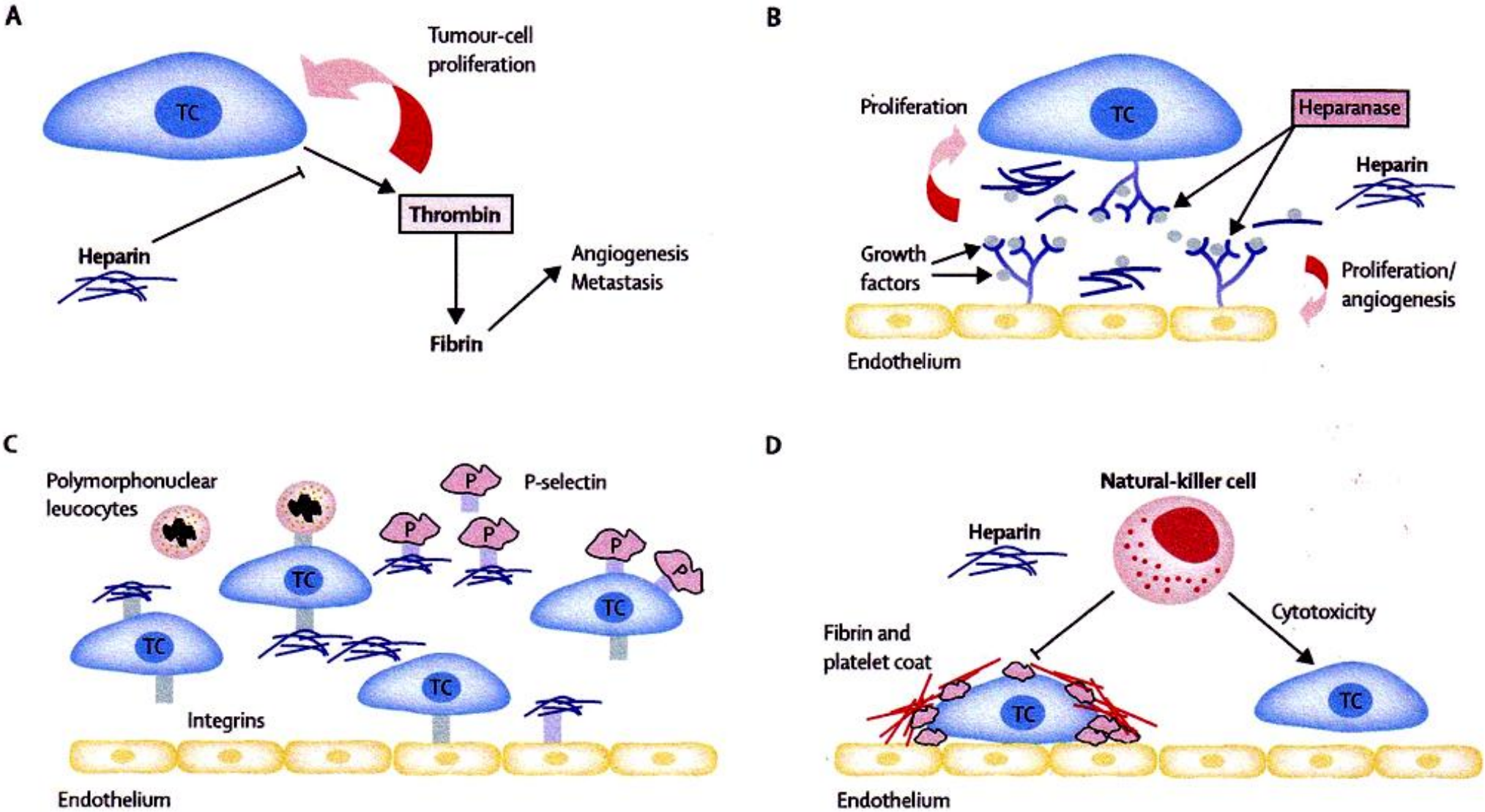
Akl et al Cochrane Database Syst Rev 2014; 7:CD006650.

HETEROGENEITE DES HBPM

Heparin	Mean MW (Da)	Anti-Xa/ anti-IIa	Anti-Xa activity/mg
UFH	15000	1	193 UI
Tinzaparin	6500	1.8	90 IU
Dalteparin	6000	2.5	160 IU
Enoxaparin	4500	3.6	100 IU
Nadroparin	4300	3.2	95–130 IU
Reviparin	3800	3.25	106 IU
Bemiparin	3600	9	80 IU

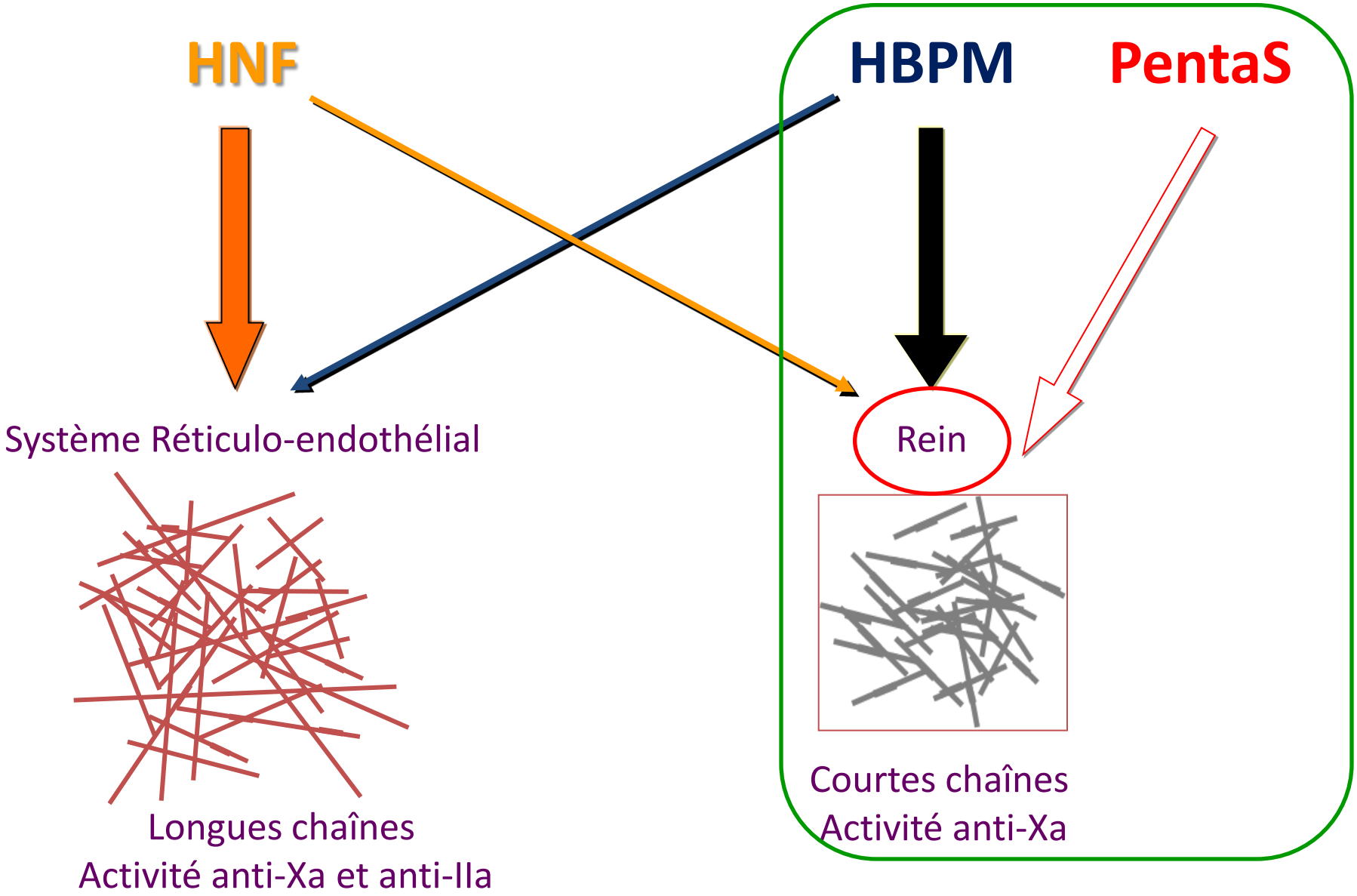
European Pharmacopoeia 2010

HBPM ACTIONS MULTIFOCALES ANTI-TUMORALES



Prandoni P et al. Lancet Oncol 2005;6:401–10

ÉLIMINATION DES DÉRIVÉS HÉPARINIQUES



Holbrook A et al. Chest 2012; 141(2 Suppl): e152S-e184S)

MTEV, REIN ET CANCER

Traitement curatif

- 1684 patients avec MTEV et cancer (RIETE + Leiden) :

Characteristics	eGFR > 60 mL min^{-1} N = 932	eGFR 45–60 mL min^{-1} N = 317	eGFR 30–45 mL min^{-1} N = 285	eGFR < 30 mL min^{-1} N = 150
Mean age (SD)	62.2 (14.0)	69.9 (10.5)	74.6 (10.9)	73.8 (13.2)
Male sex	507 (54.4)	202 (63.7)	162 (56.8)	73 (48.7)
Mean eGFR (SD)	95.6 (32.6)	52.4 (4.1)	37.9 (4.3)	20.8 (7.6)
VTE site				
Isolated PE	372 (39.9)	121 (38.2)	93 (32.6)	40 (26.7)
Isolated DVT	374 (40.1)	124 (39.1)	127 (44.6)	84 (56.0)
Combined PE and DVT	186 (20.0)	72 (22.7)	65 (22.8)	26 (17.3)
Hematologic cancer	84 (9.0)	31 (9.8)	31 (10.9)	14 (9.3)
Solid cancer	848 (91.0)	286 (90.2)	254 (89.1)	136 (90.7)
Disease state of malignancy				
Localized disease*	325 (34.9)	124 (39.1)	109 (38.2)	70 (46.7)
Metastatic disease*	469 (50.3)	155 (48.9)	130 (45.6)	65 (43.3)
Risk factors for VTE present prior to index VTE				
Previous VTE	65 (7.0)	30 (9.5)	26 (9.1)	12 (8.0)
Immobilization	229 (24.6)	80 (25.2)	84 (29.5)	54 (36.0)
Recent major surgery	199 (21.4)	56 (17.7)	50 (17.5)	23 (15.3)
	103 (11.1)	40 (12.6)	32 (11.2)	19 (12.7)
BMI > 30 kg m^{-2}				
Active chemotherapy	437 (46.9)	114 (36.0)	85 (29.8)	39 (36.0)
Active hormonal therapy†	6 (0.6)	1 (0.3)	3 (0.7)	2 (1.3)
	55%	19%	**17%**	**9%**

Kooiman J et al JTH 2013

LIMITES DE L'AVK

- Fenêtre thérapeutique étroite TTR < 50%
  => INR difficile à maintenir à niveau approprié

- Nombreuses interactions alimentaires et médicamenteuses
  => fluctuations redoutées

- Polymorphismes génétiques
  => 60% des instabilités constatées

- Fréquents vomissements et troubles digestifs chimio-induits
  => pharmacodynamie variable.

- Glossites et dysphagies ou mycoses fréquentes
  => prise orale et la gestion de ce traitement oral compliquées

- Métabolites des AVK à clairance rénale
  => INR instable chez les cancéreux insuffisants rénaux

AVK ET INSUFFISANCE RENALE : ASSOCIATION RISQUÉE

- **EFFETS DÉLÉTÈRES CONNUS SUR LA FONCTION RÉNALE :**

  NÉPHRITE INTERSTITIELLE

  VASCULARITES

  HÉMORRAGIES GLOMERULAIRES

  HYPOALBUMINÉMIE : ↑ INR ÉLEVÉ INSTABLE

http://www.kidney-international.org original article

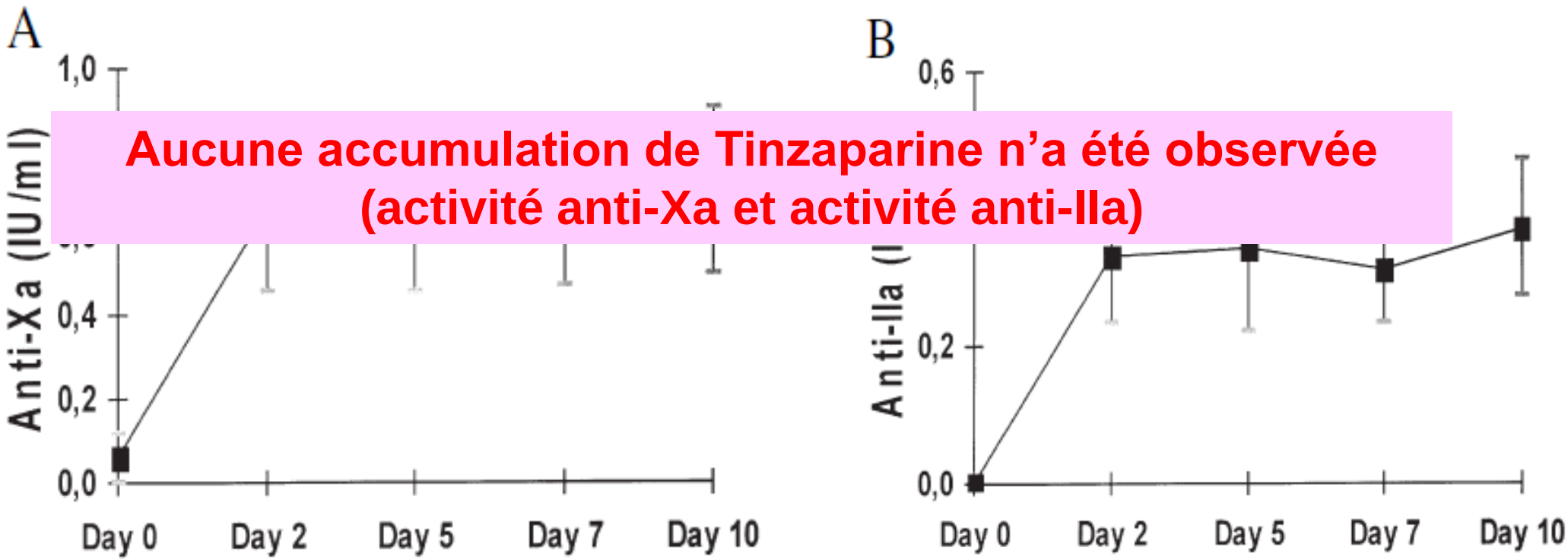
Warfarin-related nephropathy occurs in patients with and without chronic kidney disease and is associated with an increased mortality rate

Sergey V. Brodsky[1], Tibor Nadasdy[1], Brad H. Rovin[2], Anjali A. Satoskar[1], Gyongyi M. Nadasdy[1], Haifeng M. Wu[1], Udayan Y. Bhatt[2] and Lee A. Hebert[2]

Kidney International (2011) **80,** 181–189

Limdi NA et al., J Am Soc Nephrol 2009

TINZAPARINE ET SUJETS VULNÉRABLES



Aucune accumulation de Tinzaparine n'a été observée (activité anti-Xa et activité anti-IIa)

N=30 pts (6H/24F),

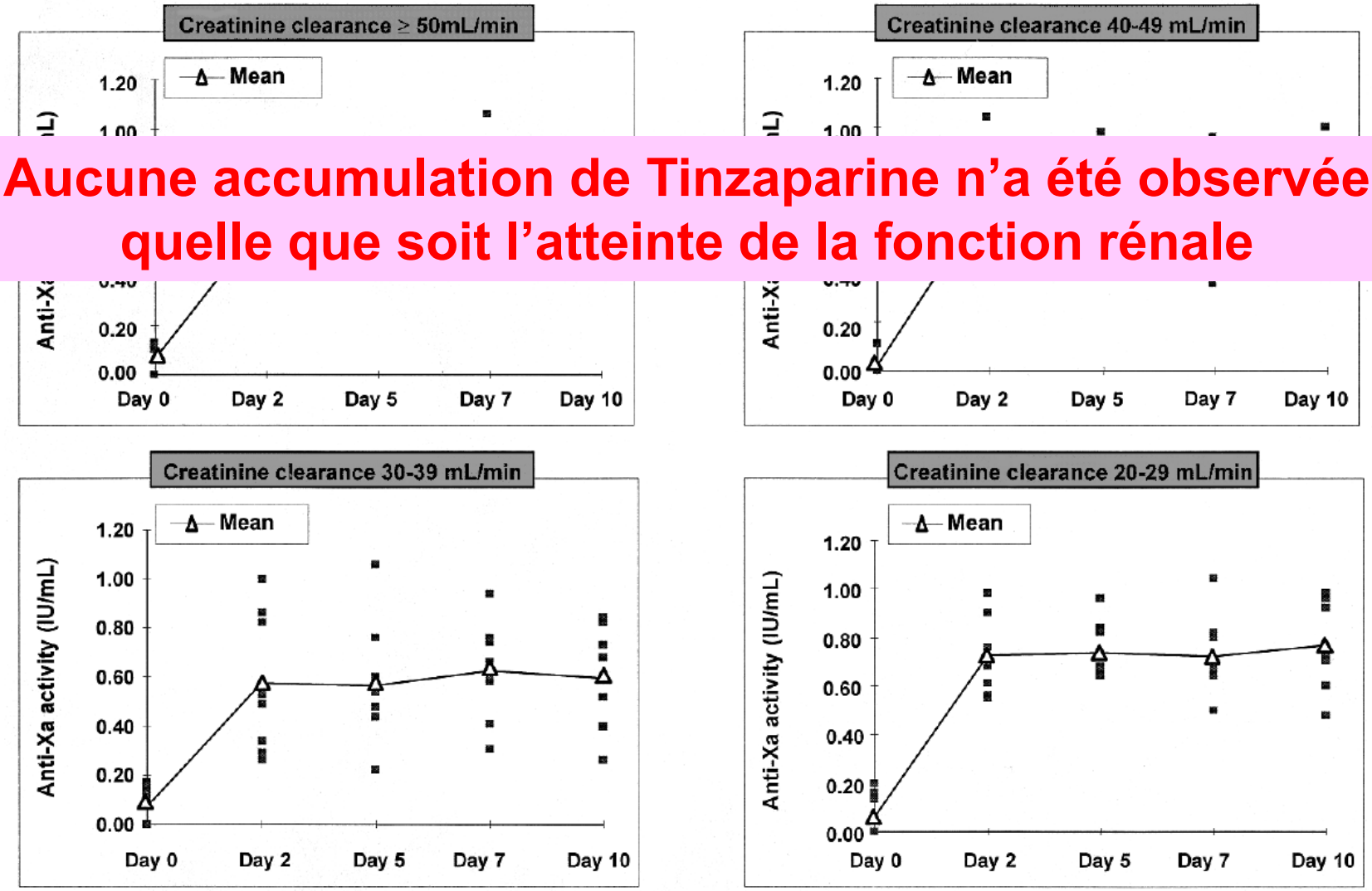
Tinzaparine 175 UI/kg pendant 10 jours, 62.7 ± 14.6 kg (38-90)

âge moyen 87±5.9 ans (71-96) clairance très altérée 40.6 ± 15.3 ml/min (20-72)

Siguret et al. Thromb Haemost 2000; 25 : 725-33

TINZAPARINE ET SUJETS VULNÉRABLES

Aucune accumulation de Tinzaparine n'a été observée quelle que soit l'atteinte de la fonction rénale



Siguret et al. Thromb Haemost 2000; 25 : 725-33

TINZAPARINE ET SUJETS VULNÉRABLES

N=200 patients

175 UI/kg pendant # 1 mois,

Âge moyen 85,2 ± 6,9 ans

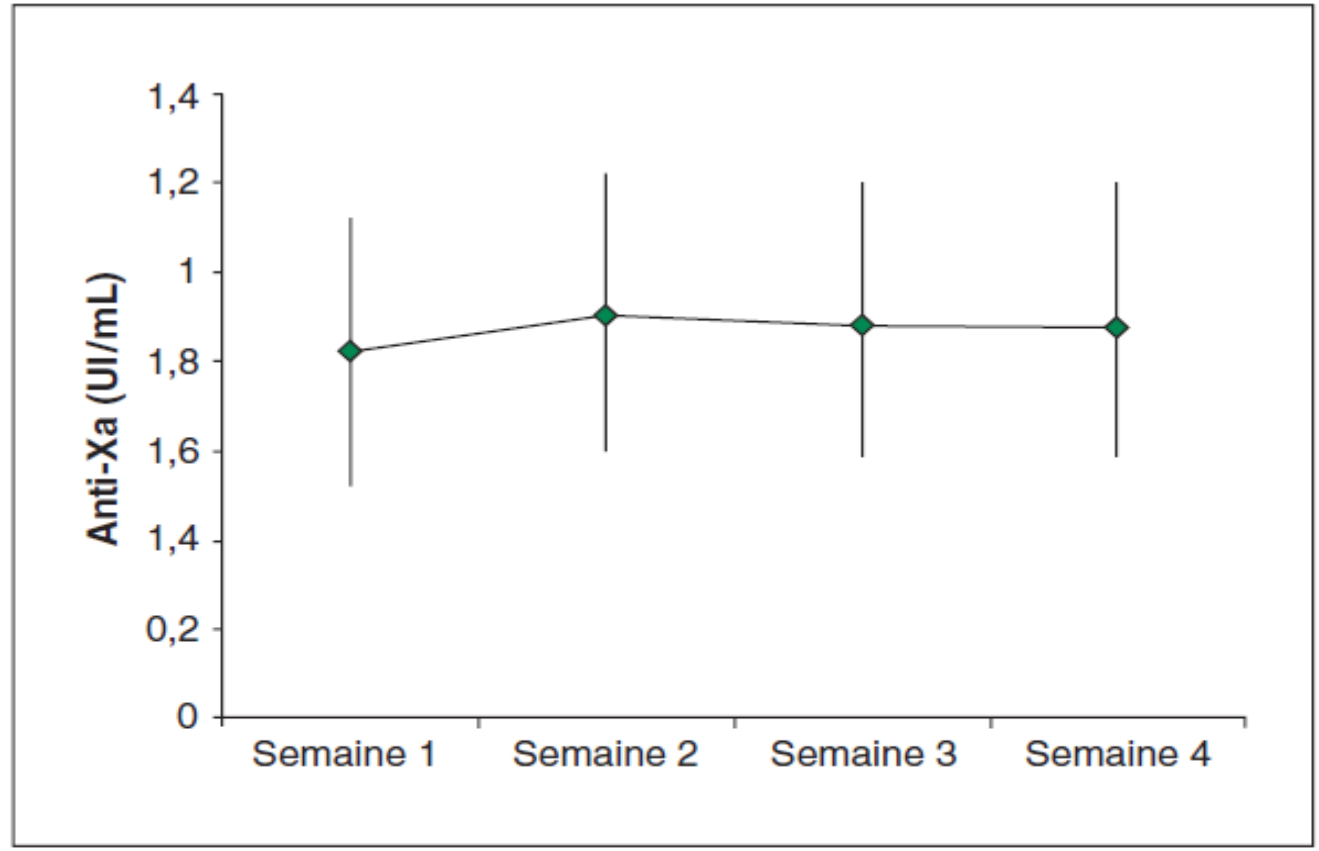
Clairance moyenne altérée

Clcr 51,2 ± 22,9 ml/min

25% des pts ont une

Clcr 20 à 35 ml/min

Poids moyen 58 ± 14 kg



Aucune accumulation de Tinzaparine n'a été observée
(activité anti-Xa et activité anti-IIa)

1 seule hémorragie fatale (co-morbidités+++)

Pautas E et al. Drug Saf 2002 ; 25 : 725-33

ENOXAPARINE CURATIF ET SUJETS VULNÉRABLES

Characteristic	Mean		
	Major Bleeding (n = 19)	No Major Bleeding (n = 145)	*P* Value
Length of enoxaparin sodium therapy, d	18.0	11.7	.03
Age, y	70.3	65.9	.14
Female sex, %[a]	40.0	60.0	.04
Weight, kg	85.7	94.8	.08
SCr level, mg/dL	1.3	1.0	.003
CrCl, mL/min[b]	57.5	85.3	.002
Platelet count, $<100 \times 10^3/\mu L$	18.8	2.8	.008
Baseline INR	2.18	1.62	.006
Highest INR during enoxaparin therapy	2.64	2.74	.76
Concomitant therapy, %			
Aspirin	78.9	51.7	.02
Clopidogrel bisulfate[b]	5.3	9.7	.53
Warfarin	89.5	89.7	.98
Total No. of bleeding risk factors	1.4	1.5	.99

Hémorragies Majeures

6/105 pts (5.7%) si Clcr ≥80 vs

13/59 pts (22.0%) si Clcr 30-50

OR 4.7 (95% CI, 1.7-13.0; *p*=0.002).

DeCarolis D et al Arch Intern Med 2012 ; 172 (22) : 1713-1718

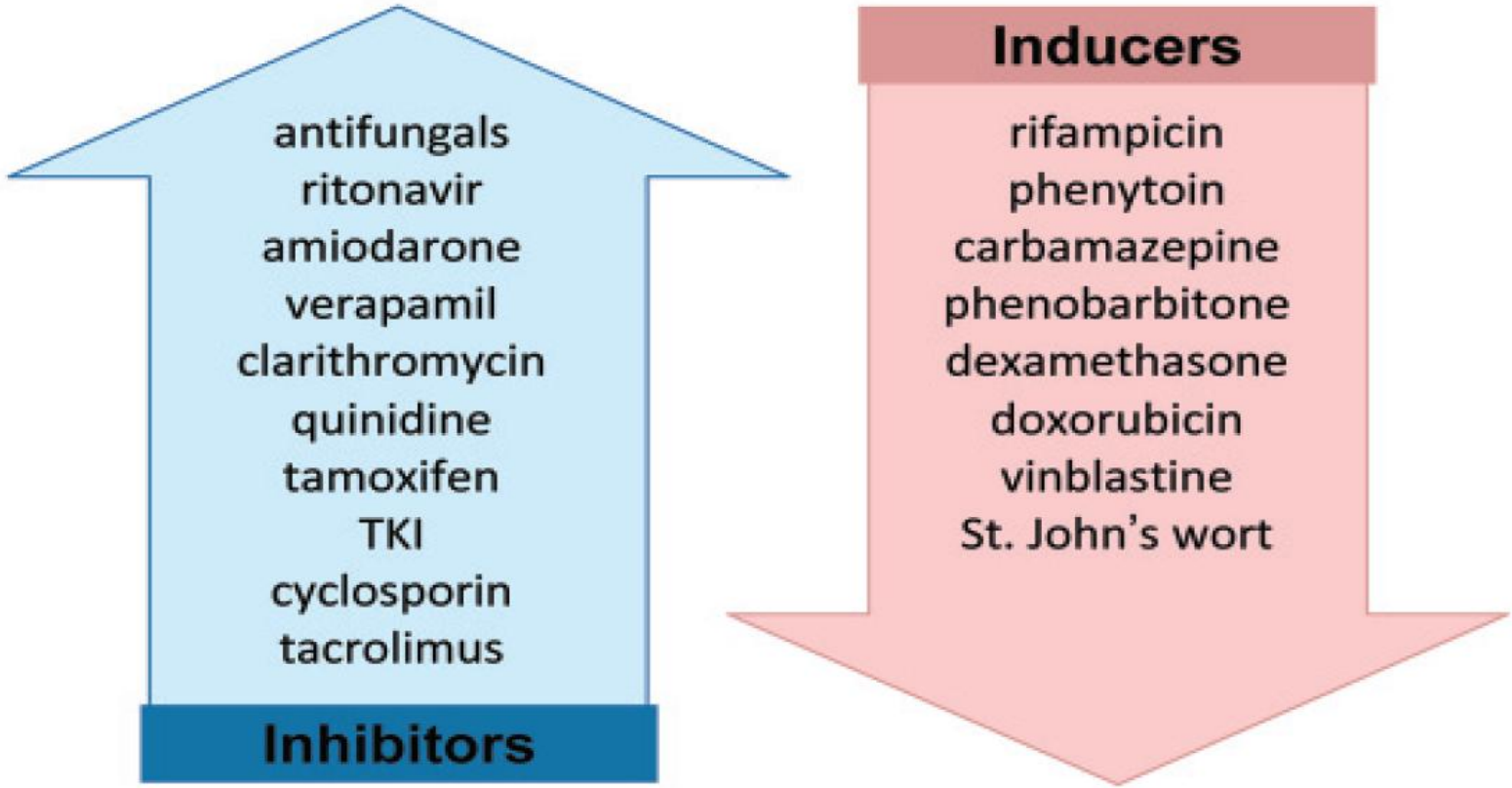
ANTICOAGULANTS ORAUX DIRECTS (AOD)

	Dabigatran[1]	Rivaroxaban[1,2]	Apixaban[1,3]	Edoxaban[4-6]
Cible	IIa	Xa	Xa	Xa
Cmax	1.25-3	2-4	3-4	1-2
CYP métabolisme	Non	2/3 (3A4-2J2)	½ (3A4)	<4%
Biodisponibilité	6.5%	80-100%	50%	62%
Transporteurs	P-gp	P-gp/BCRP	P-gp/ BRCP	P-gp
Liaison Protéines	35%	93%	87%	50%
Demi-Vie	12-14h	9-13h	8-15h	8-10h
Clairance rénale	80% (active)	33% (active)	27% (active)	50% (active)
Mode de prise	BID	BID/QD	BID	QD

BCRP = breast cancer resistance protein
CYP = cytochrome P450; P-gp = P-glycoprotein

1. Eriksson BI et al. Clin Pharmacokinet 2009; 48: 1-22; 2. Xarelto [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2011;
3. ELIQUIS Summary of Product Characteristics. Bristol Myers Squibb/Pfizer EEIG, UK; 4. Ruff CR et al. Am Heart J 2010;160:635-641;
5. Matsushima et al. Am Assoc Pharm Sci 2011; abstract; 6. Ogata et al. J Clin Pharmacol 2010;50:743-753

INTERACTIONS POTENTIELLES ANTI-CANCÉREUX ET AOD



Lee et al Thromb Res 2014; 133 : S167-S171

			DOA	LMWH/VKA
RECOVER 1-2 6 months FU	Total N=4772	VTE Rec. Major Bleed.	2.4% 0.8%	2.1% 1.4%
Dabigatran 150mg x 2/d	**Cancer** N=334 (7%)	VTE Rec. Major Bleed. MB + CRNMB*	**5.8%** **3.8%** **14.5%**	**7.4%** **4.6%** **13.2%**
EINSTEIN 6 months FU	Total N=8862	VTE Rec. Major Bleed.	2.1% 1.0%	2.3% 1.7%
Rivaroxaban 15mg x 2/d and 20mg/d	**Cancer** N=430 (4.8%)	VTE Rec. Major Bleed. MB+CRNMB	**2.5%** **2.6%** **13.5%**	**4.0%** **4.1%** **12.0%**
HOKUSAI VTE 12 months FU	Total N=8292	VTE Rec. CRB*	3.2% 8.5%	3.5% 10.3%
Edoxaban 60mg/d	**Cancer** N=771 (9,2%)	VTE Rec. CRB MB +CRB	**3,7%** **12.4%** **18.3%**	**7,1%** **18.8%** **25.3%**

CRNMB Clinically Relevant Non Major Bleeding
CRB : Clinically Relevant Bleeding (Major and Non-Major)

van der Hulle J Thromb Haemost 2014; 12:1116–1120
Vedovati et al Chest 2014 in press.

AOD DANS THROMBOSE ET CANCER?

- Patie ns+++
  (usées…)
- Fréqu
- Trou té?

- **Peu ations sur les c ++…)**
- **Com**
- **Pas potentielles**
- **Anal la vraie vie**
- **Essa**

Lee & Carrier Thromb Res 2014; 33: S167-S171

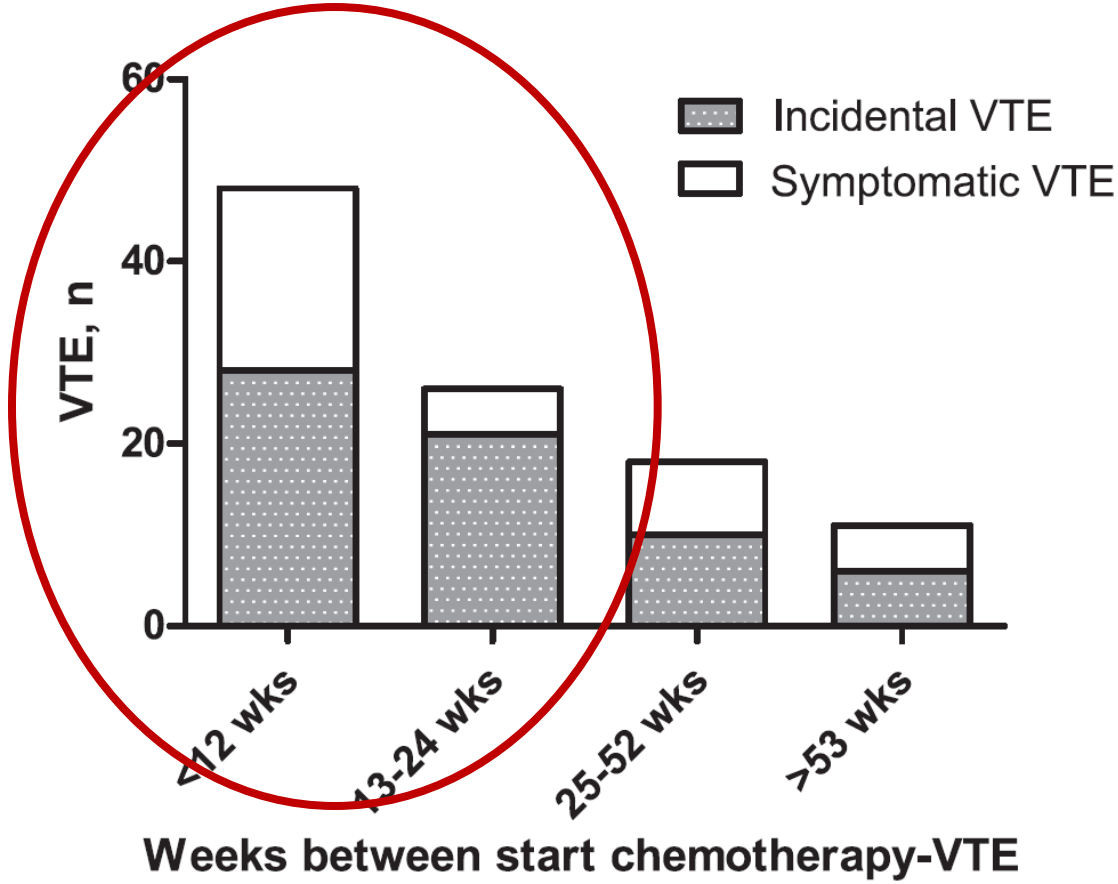
4.6 Use of novel oral anticoagulants for either prevention or treatment of VTE in patients with cancer is not recommended at this time.	Evidence: insufficient Recommendation type, strength: informal consensus, strong
4.7 Based on consensus, incidental PE and DVT should be treated in the same manner as symptomatic VTE. Treatment of splanchnic or visceral vein thrombi diagnosed incidentally should be considered on a case-by-case basis, considering potential benefits and risks of anticoagulation.	Evidence: insufficient Recommendation type, strength: informal consensus, moderate
Anticoagulation and survival	
5.1 Anticoagulants are not recommended to improve survival in patients with cancer without VTE.	Evidence: weak to moderate Recommendation type, strength: informal consensus, moderate
5.2 Patients with cancer should be encouraged to participate in clinical trials designed to evaluate anticoagulant therapy as an adjunct to standard anticancer therapies.	

Lyman et al J Clin Oncol 2013

« INCIDENTAL THROMBOSIS »
THROMBOSE DE DÉCOUVERTE FORTUITE

>2/3 avant le 6ème mois

Risque x 3 :
Métastases
↑Leucocytes
Cys-Platine



Incidence croissante
Mêmes risques qu'EP ∑que
Etude en cours NCT01727427
(30 centres)

Di Nisio et al Thromb Haemost 2010; 104:1049-1054
Van Es et al Thromb Res 2014; 133: S172-S178

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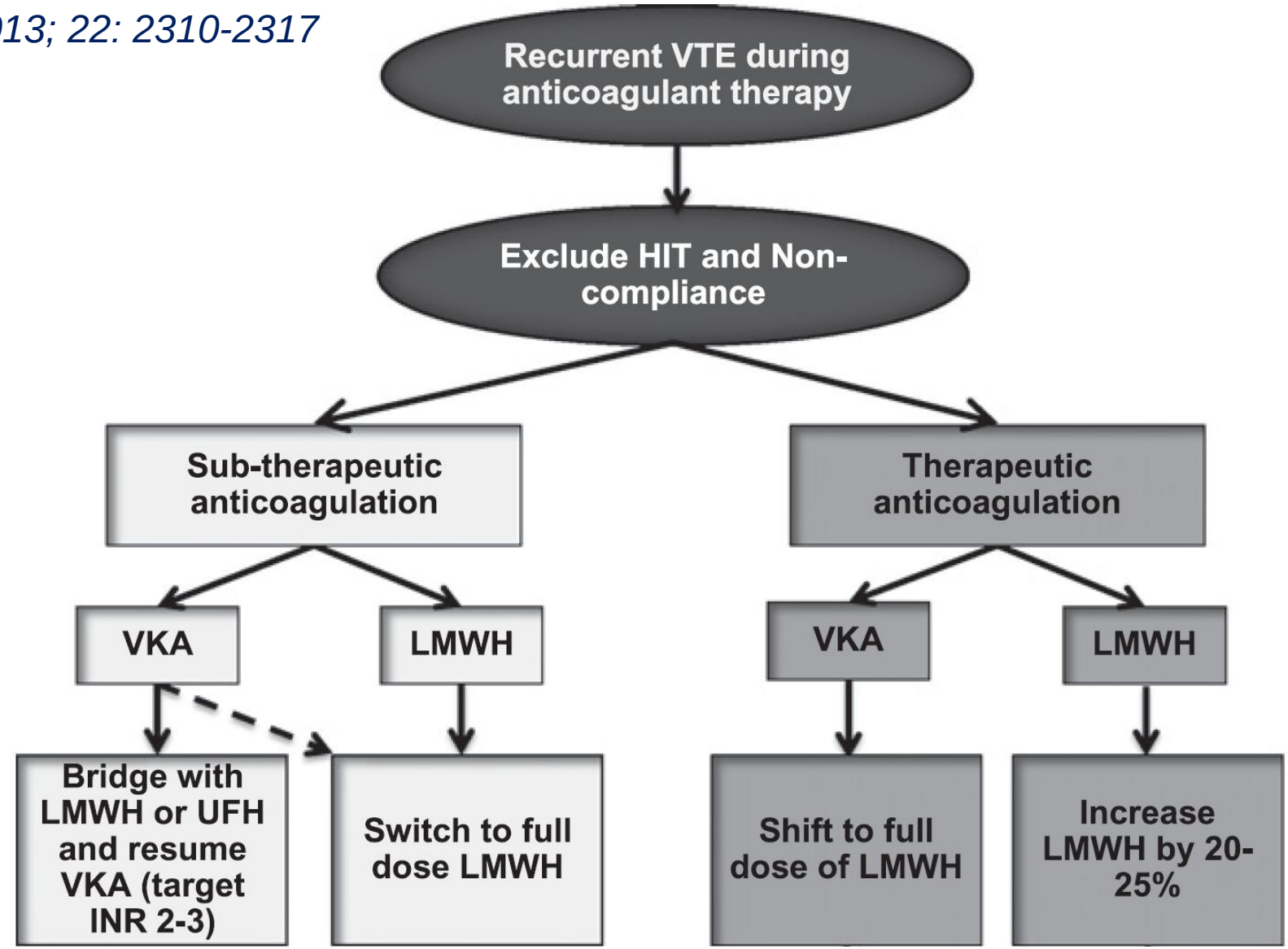
Lyman et al J Clin Oncol 2013; 31: 2189-2204

EN CAS DE RECIDIVE SOUS TRAITEMENT?

Lee et al Blood 2013; 22: 2310-2317



SURVEILLANCE PLAQUETTES ET CANCER

Contexte chirurgical ou traumatique récent (≤3 mois) :

- numération plaquettaire avant le traitement par HBPM ou au plus tard dans les 24 heures après l'instauration du traitement,
- puis 2 fois par semaine pendant un mois (période de risque maximal),
- puis une fois par semaine jusqu'à l'arrêt du traitement en cas de traitement prolongé.

En dehors d'un contexte chirurgical ou traumatique récent :

surveillance systématique (mêmes modalités que ci-dessus) chez :

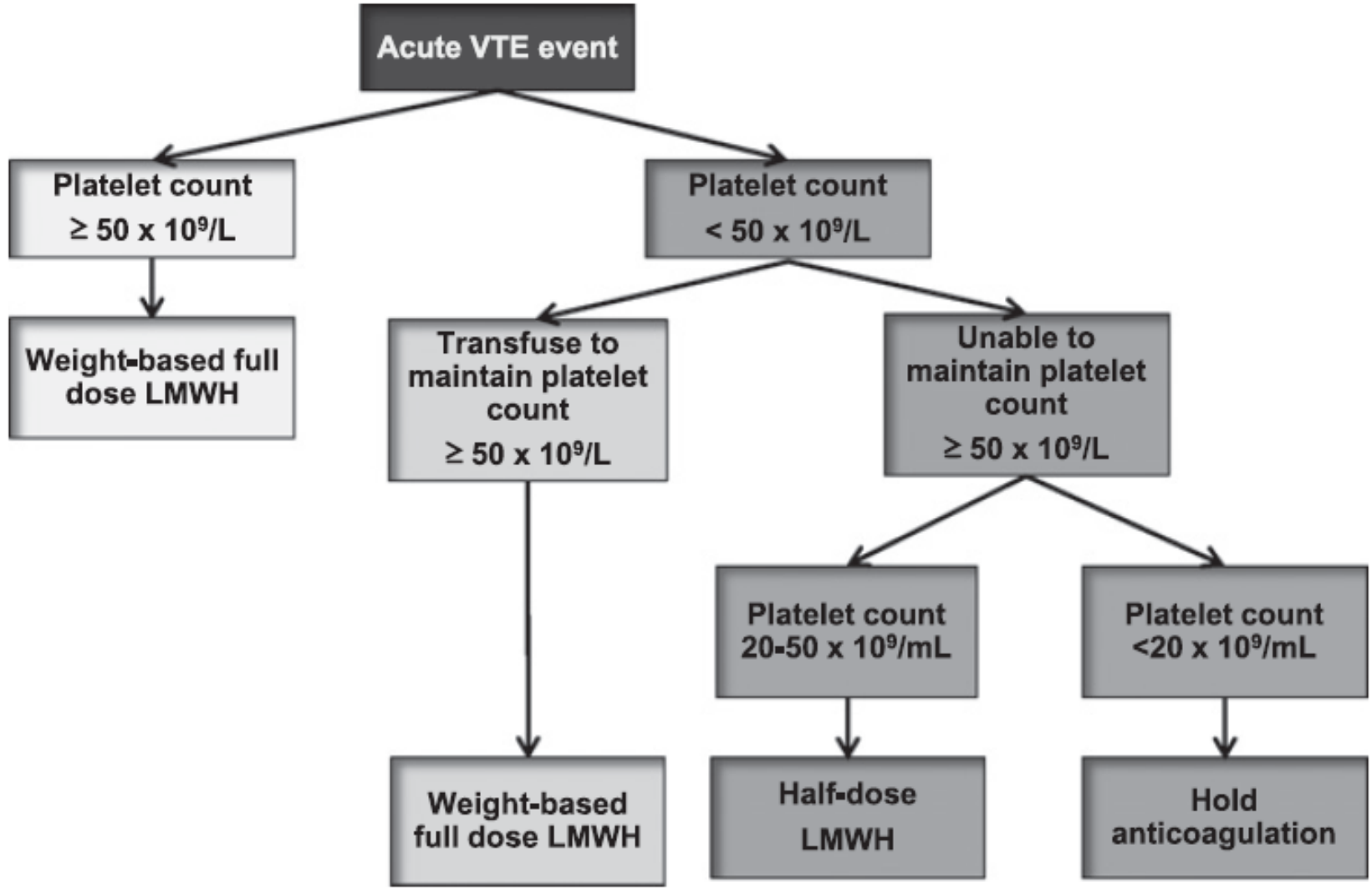
- ayant des antécédents d'exposition à l'HNF ou aux HBPM dans les 6 derniers mois, compte tenu de l'incidence des TIH > 0.1 %, voire >1 %,
- atteints de comorbidités importantes, compte tenu de la gravité potentielle chez ces patients.

HAS 2009

Farge et al J Thromb Haemost 2013; 11: 56-70;

Lyman GH et al. J Clin Oncol 2013; 31: 2189-2204

EN CAS DE THROMBOPENIE?



Lee et al Blood 2013; 22: 2310-2317

ADHERENCE TO GUIDELINES FOR THE TREATMENT OF VENOUS THROMBOEMBOLISM IN CANCER PATIENTS

- RIETE registry : 2945 CAT pts => **51%** received LMWH at 3 months

  Monreal et al J Thromb Haemost 2006; 4: 1950-1956

- Multicenter Advanced Study for a ThromboEmbolism Registry (MASTER) 424 CAT pts => **64%** received VKA

  Imberti et al Haematologica 2008; 93: 273-278

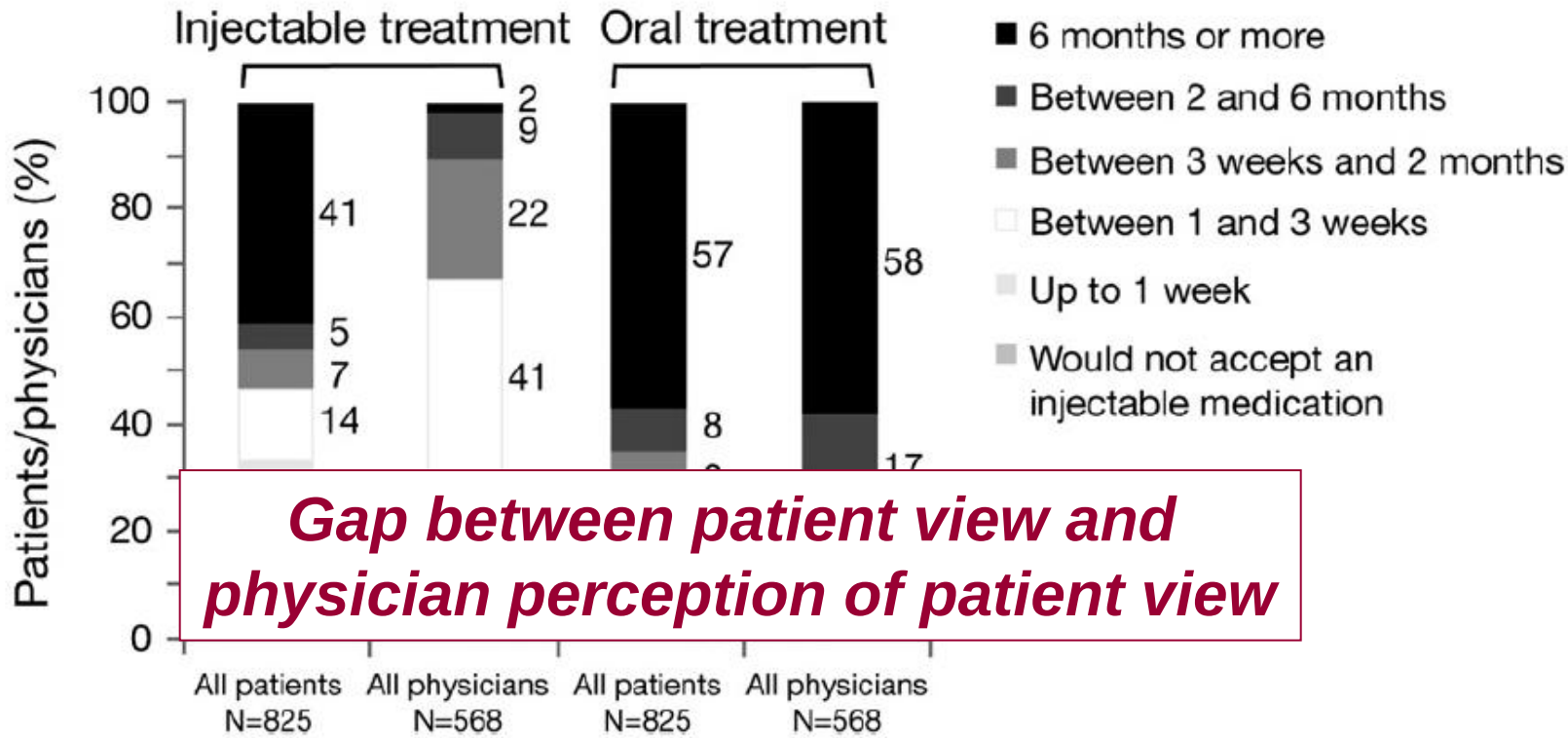
- CARMEN study 500 CAT pts => **59%** adequate anticoagulation

  Sevestre et al J Clin Oncol 2012; 30 (suppl) 1580

PERCEPTIONS DES MEDECINS ET LEURS PATIENTS SUR LA VOIE D'ADMINISTRATION DE L'ANTICOAGULANT

568 médecins et 825 patients de 5 pays

Q: Generally, for how long would you agree to be treated with an injectable/oral medication that was prescribed by your physician?



Gap between patient view and physician perception of patient view

Cimminiello et al Thromb Res 2012; 129: 139-145

IMPACT DE LA MTEV… OUI
VERBATIMS…

- **Impact majeur sur leur vie quotidienne** :
  …autonomie réduite… activités basiques difficiles

- **Entité distincte de la maladie cancéreuse** :
  … EP assombrit le contexte … plus grande détresse et on craque!

- **Symptomatologie terrible de l'EP** :
  …expérience angoissante, sensation de mort imminente!

- **Diagnostic d'EP** :
  … choc supérieur au diagnostic de cancer …
  … éclipse l'expérience négative du K

Seaman et al Patient Preferences and Adherence 2014; 8 : 453-461

ACCEPTABILITE DES HBPM… OUI
VERBATIMS…

- **Rapport bénéfice/risque démontré** :
  …contrainte acceptable et acceptée…
- **Protection par injection quotidienne sous-cutanée** :
  … compromis pour éviter les récidives
- **Observance respectée** : *…rituel pour systématiser l'injection*
- **Tolérance optimisée** : *… ecchymoses minimes ou fibrose limitée aux points d'injections … injections multisites cycliques*
- **Confiance et pragmatisme** *: …se débrouiller pour continuer!*

Seaman et al Patient Preferences and Adherence 2014; 8 : 453-461

CONCLUSION

- **Cancer => Hypercoagulabilité acquise naturelle et variable**
- **Processus thrombotique <=> Prolifération tumorale**
- **HBPM : 1er choix en phase aiguë et à long terme**
- **Défaut d'implémentation des bonnes pratiques**
- **Education +++ => Optimisation thérapeutique**
  Efficience économique
  Amélioration de la Qualité de Vie

« CANCER ET THROMBOSE : DUALITÉ NOTOIRE…
… TUE L'ALITÉ ET L'AMBULATOIRE