Référentiels inter régionaux
en Soins Oncologiques de Support

Cancer and Venous Thrombo-Embolism (VTE): AFSOS Guideline

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Faculty Disclosure

Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*
Leo Pharma	X	X						
Pfizer	X	X						
Amgen	X	X						
Roche	X							
Vifor Pharma	X	X						
Novartis	X							

2018
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SUPPORTIVE CARE IN CANCER

Real Disclosure

Public Declaration of Interests 2016 Update

- Pr Ismail Elalamy:

  - Essais cliniques : Mitsubishi Pharma, Shire , Pfizer, Sanofi-Aventis, GSK, Leo-Pharma

  - Consultant: Daiichi Sankyo, BMS, NovoNordisk , Mitsubishi Pharma , Shire , Boehringer-Ingelheim, Celgène , Pfizer, Bayer HealthCare, Astra-Zeneca, Sanofi-Aventis, GSK, LFB, Leo-Pharma

- Pr Isabelle Mahé:
  - Projet de recherche: Leo;
  - Consultant: Daiichi Sankyo, BMS; Leo
  - Orateur: Leo Pharma, Bayer, Boehringer, BMS
- Dr Didier Mayeur:
  - Orateur: Leo Pharma
- Pr Guy Meyer:

  - Essais cliniques : en qualité de co-investigateur, expérimentateur non principal, collaborateur à l'étude : Daiichi Sankyo ; Bayer ; Sanofi Aventis ; Leo Pharma

  - Interventions ponctuelles : activités de conseil non rémunérées : Bayer, Leo Pharma

  - Conférences : invitations en qualité d'intervenant non rémunérées : Leo Pharma ; Sanofi Aventis ; Boehringer-Ingelheim, Bayer

  - Conférences : invitations en qualité d'auditeur (frais de déplacement et d'hébergement pris en charge par une entreprise) : Leo Pharma ; Boehringer-Ingelheim ; Bayer ; Daiichi Sankyo

  - Subventions à la recherche versées à mon établissement hospitalier : Leo Pharma, Boehringer-Ingelheim, Bayer

Summary

Méthodology

- Initial work made by the ONCORA network.
- Muldisciplinary workshop (general medicine, internal medicine, oncology, vascular pathology)
- Assessment of the available recommendations (ACCP, ASCO, AIOM, ISTH, NCCN, SOR) with the AGREE grid
- Adjustment of the recommendations with the ADAPT method then shaping in the ONCORA format 2009

- External reviewing by ONCORA members 2009
- Formal validation during the inter regional cancer network oncologic supportive care workshop (ONCORA / ONCOLOR; Lyon, July 2009)
- Updates in 2011, 2013 and 2016

Targeted Population

Knowing that cancer is a risk factor for VTE

Patients

Aged over 18 with cancer or haematological malignancie:

• With VTE. *Superficial vein thrombosis are not concerned by this guideline*

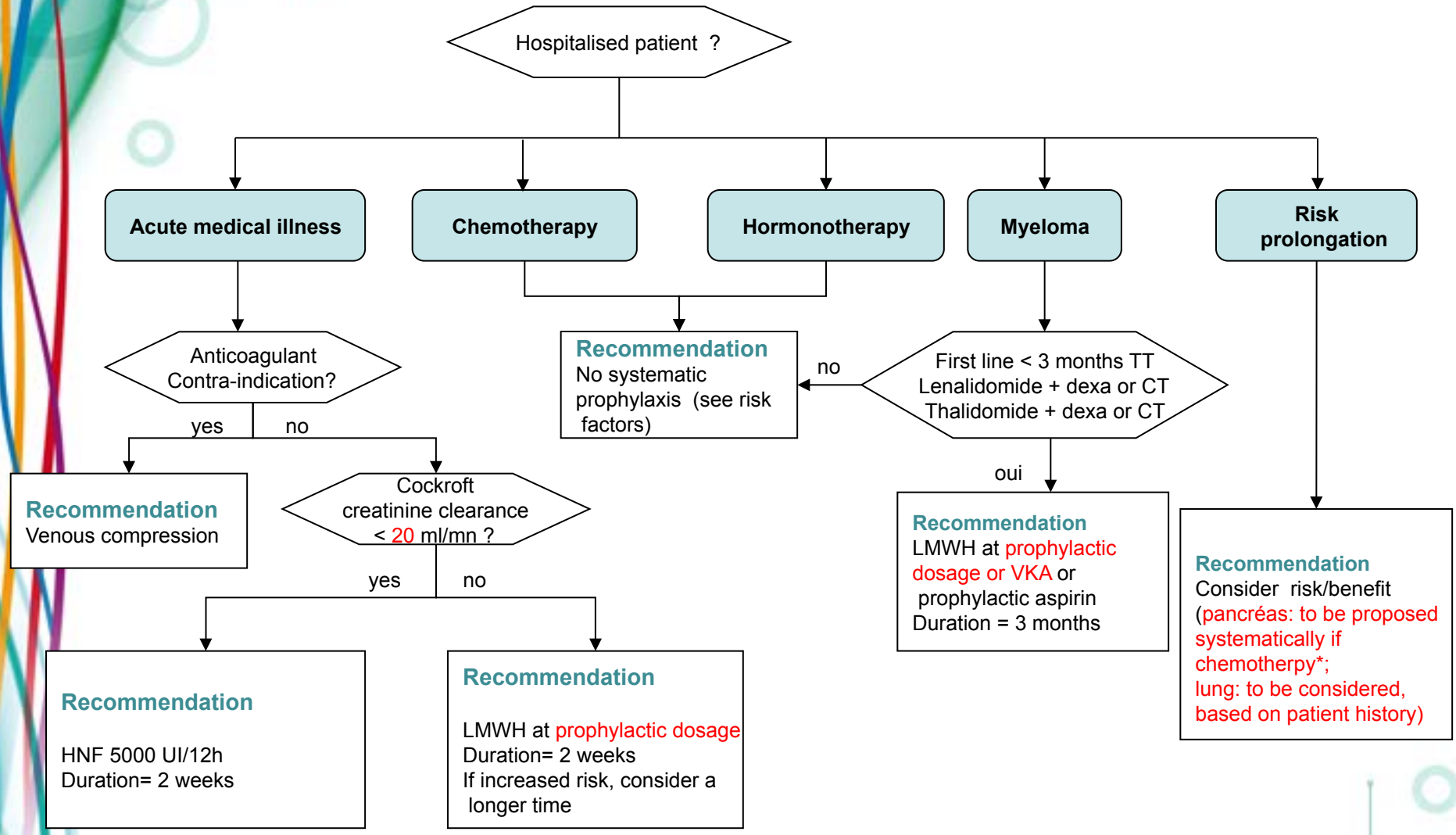
• Or at risk of VTE by:

Bedridden patient
Surgical patient
Hospitalised patient
Treatment at VTE risk
Presence of a central venous catheter (> 3 weeks) in superior vena cava or with implanted device*. Femoral catheter or PICC lines are not concerned by this guideline*

Healthcare Professionnals

• Members of the ONCORA network
• General practitionners and specialised physicians treating VTE during cancer
• Paramedical staff treating VTE during cancer

Primary prevention of the VTE, except catheter, in medical environment, during hospitalization



*: The prophylactic dosage used in Conko 004 trial is enoxaparin 1 mg/kg

Prevention in out-patients : the Khorana score

Pimary VTE prophylaxis during chemotherapy in out-patients

Currently, there is no indication of systematic thromboprophylaxis.It will be decided case by case, considering the risk/benefit balance (thrombosis risk due to cancer and patient background) and the haemorrhagic risk (LMWH).

The Khorana score stratifies the VTE risk in out-patients treated with chemotherapy

- stomach or pancreatic cancer = 2 pts
- lymphoma, lung, bladder, testi, gynecologic pelvis = 1 pt
- platelets> 350 G/L = 1 pt
- Hb < 100 g/L or ESA = 1 pt
- WBC > 11 G/L = 1 pt
- BMI > 35 = 1 pt

Low risk (score = 0) → VTE 0,3 % to 0,8 %
Moderate risk (score = 1 ou 2) → VTE 1,8 % to 2 %
High risk (score > 2) → VTE 6,7% to 7,1 %

This score may be useful for decision making during multidisciplinary boards;

There is no validated haemorhragic scoreduring VTE and cancer. Nevertheless, it is possible to use the Hemorr$_2$hages score . Appendice 1

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Multiple Myeloma under thalidomide or lenalinomide with chemotherapy and/or dexamethasone

Facteurs de risque

Obesity (BMI>30)	Heart or renal failure	Surgery(< 6 weeks)	ESA
History of VTE	Diabetes	Anesthesia	
Central catheter	Acute infection	Trauma	
Congenital thrombophilia	Bedridden	Prolonged trip	

≤ 1 risk factor

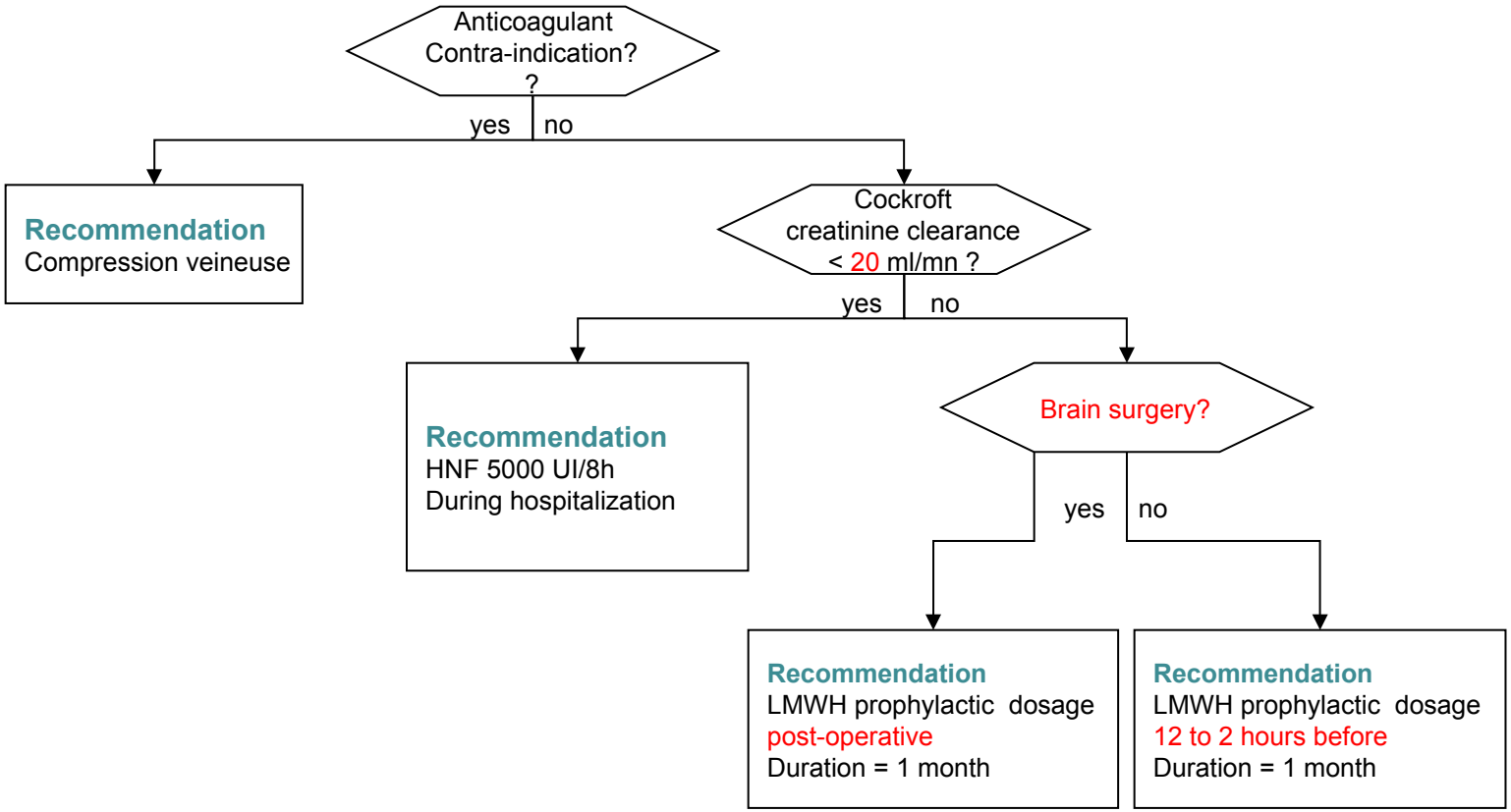
Recommendation:s
Aspirin 75-325 mg/jday
or
LMWH prophylactic dosage*
Duration 3 to 6 months ?

≥ 2 risk factors

Recommendations:
LMWH prophylactic dosage*
or
VKA (INR 2-3)
Duration 3 to 6 months ?

Plat≤ 50G/L : stop aspirin or ↓ 50% LMWH
Plat ≤ 20 G/L : stop LMWH

Primary prevention of the VTE, except catheter, in surgical environment



Primary prophylaxis of the catheter thrombosis in superior vena cava

Cf référentiel AFSOS: http://www.afsos.org/wp-content/uploads/2016/09/abord_veineux_AFSOS_V2.pdf

1- Material and placing of the catheter

- Catheter with Groshong = catheter without Groshong
- Insertion on the right side except in case of right breast cancer côté droit , unique right lung, recent right venous central catheter and patient willingness
- Ultrasound venous location indispensable if percutaneous puncture
- Catheter distal extrimity at the junction superioir vena cava- right auricle
- in case of mediastinal mass > 6 cm, no insertion of long lasting catheter in superior vena cava but consider it after an attempt of reducing the tumoral mass (corticosteroid, radiotherapy or chimotherapy on peripheric vein or temporary cent ral venous catheter)
- If possible, insertion by a trained team
- If catheter is not well positionned, ask to relocate it before use

2- Drug prophylaxis

- No indication of low-dose VKA
- No indication of prophylactic LMWH
- No heparin rinse :
  - No effect on VTE ,
  - Same efficacy of physiological serum than heparin rinse
  - Risk of HIT

Catheter malfunction ≠ catheter thrombosis

Catheter malfunction = inability to aspirate or to infuse
Malfunction causes :

- fibrin sheath
- catheter end thrombosis
- pinch off
- Catheter thrombosis

Catheter thrombosis is not always associated with malfunction sur cathéter ne se traduit pas toujours par un dysfonctionnement

Initial VTE curative treatment (< 10 days), except catheter thrombosis

usual case

Recommendation
LMWH 7 to 10 days,
then
LMWH curative
one injection per day
at-least 3 months

VTE + CI anticoagulant *

Recommendation
Inferior vena cava filter and anticoagulant as soon as possible

Patient refusal or material impossibility for long time LMWH

Recommendation
LMWH 7 to10 days
with VKA relay
beginning at D1

Cockroft creatinine clearance < 20 ml/mn ?

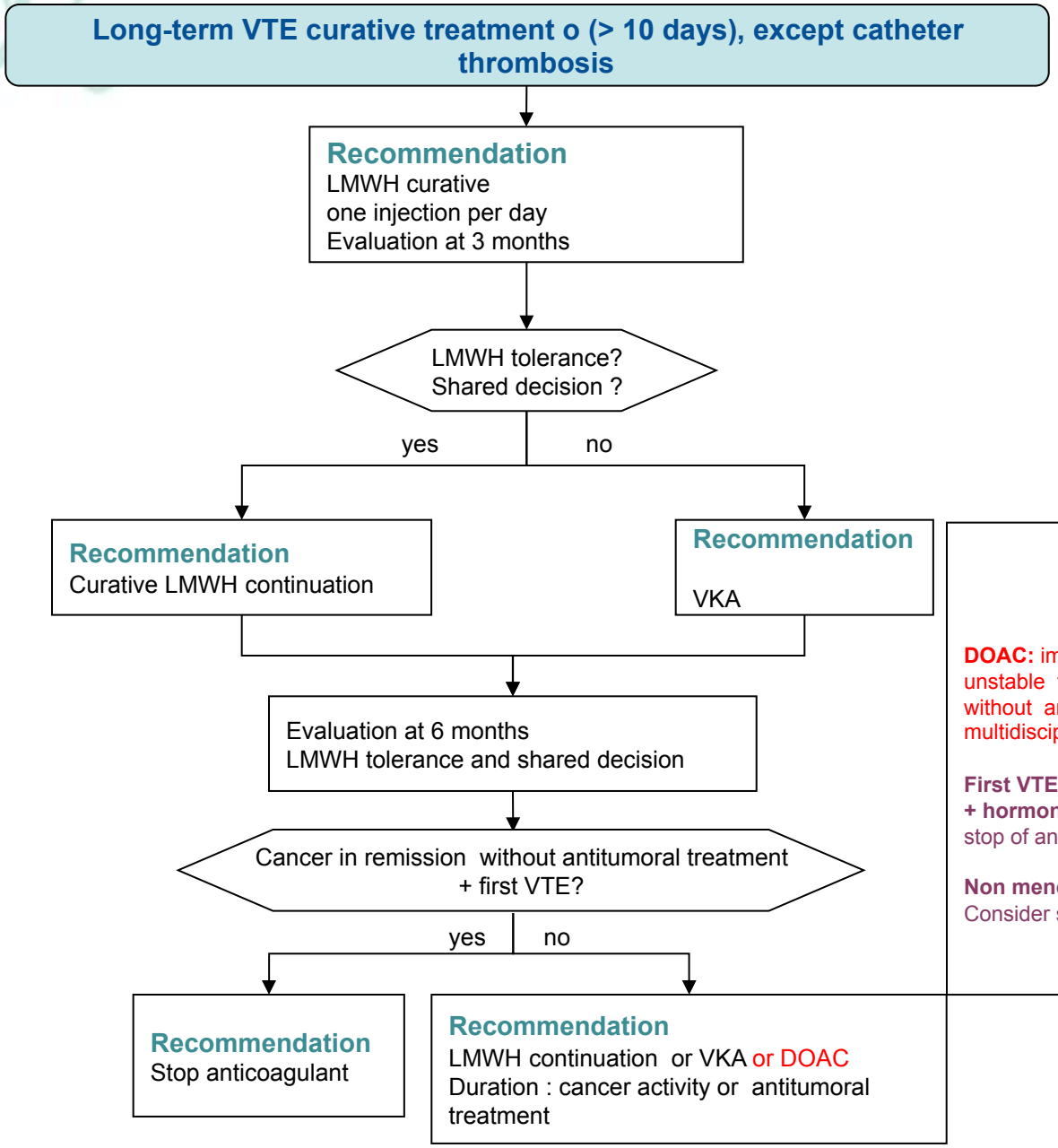
Recommendation
Unfractionned heparin :
7 to10 days
with VKA relay
beginning at D1

Pulmonary embolism with circulatory failure

Recommendation
Thrombolysis
+ Unfractionned heparin

*** Anticoagulant contra indications at curative dosage**

Recent brain surgery (< 1 month)
Haemorragic brain metastase
Haemorragic stroke (< 1 month)
Haemorragic diathesis
Haemorragic lesion
Infectious endocarditis
Pericarditis



Special situations

DOAC: impossiblility of blood sample or INR unstable to equilibrate with stable disease without antitumoral treatment and multidisciplinary board approval

First VTE + trigger factor + hormonotherapy without cancer activity : stop of anticoagulant at 6 months

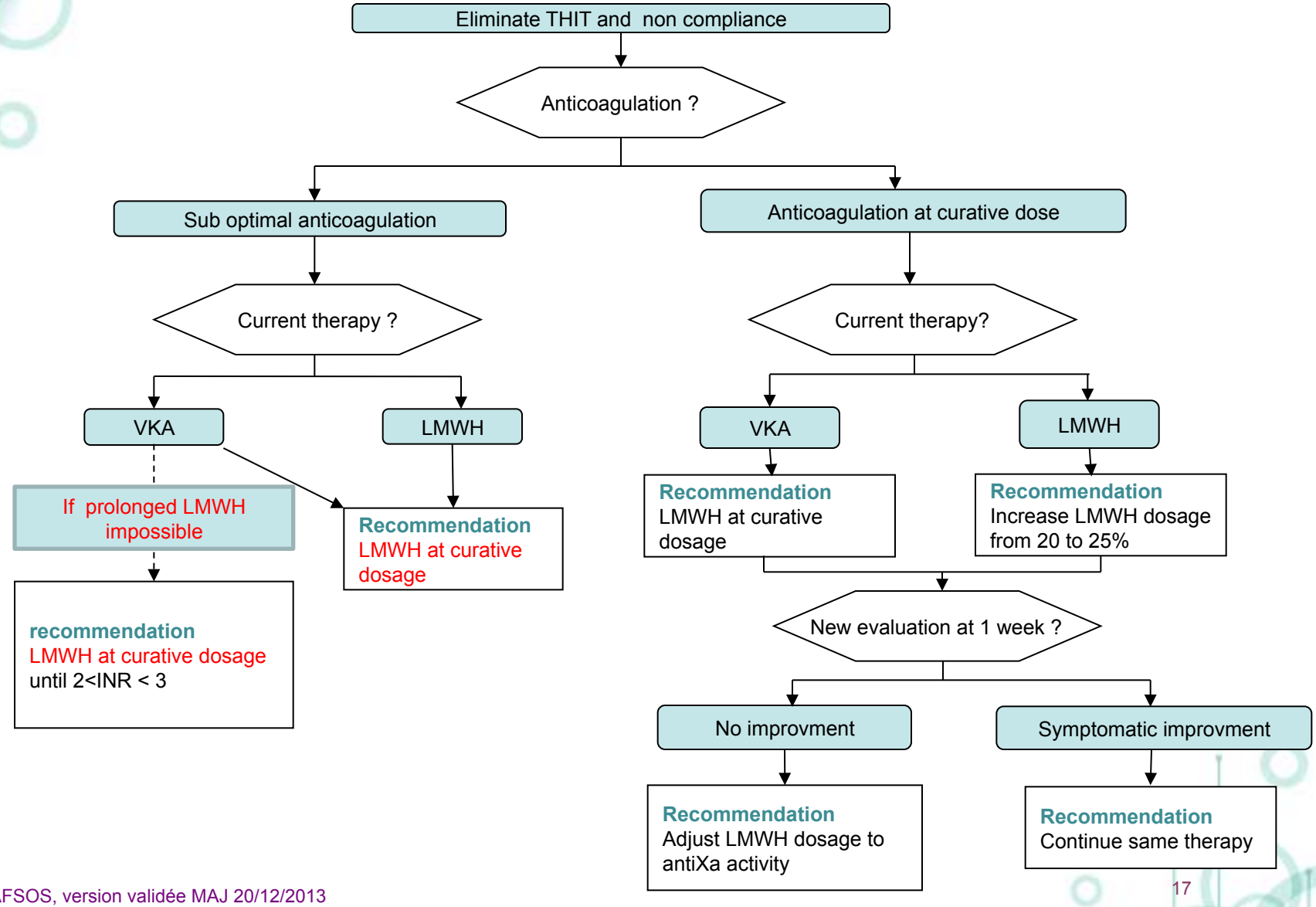
Non menopausal woman :
Consider stop oesoprogestative contraception

Louzada et al.risk recurrence

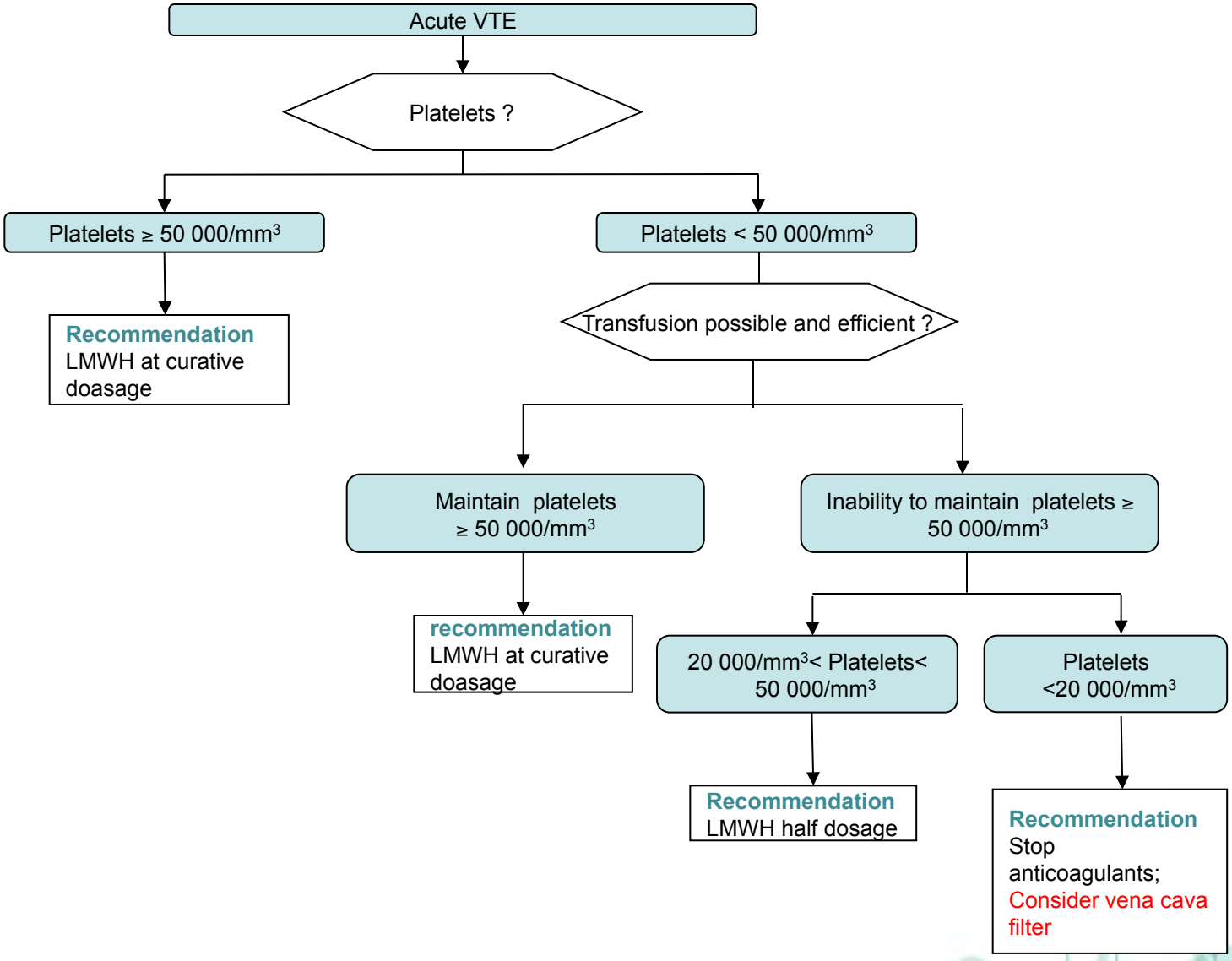
Variable	Regression Coefficient	Points
Female	0.59	1
Lung cancer	0.94	1
Breast cancer	−0.76	−1
TNM* stage I	−1.74	−2
Previous VTE	0.40	1
Clinical probability		
Low (≤0)	. . .	−3 to 0
High (≥1)	. . .	1 to 3

Score ≤0 low recurrence risk <4.5%
Score > 1 high recurrence risk ≥ 19%
Sensibilité 100%
Cohort (n=543) then validation (n=819)

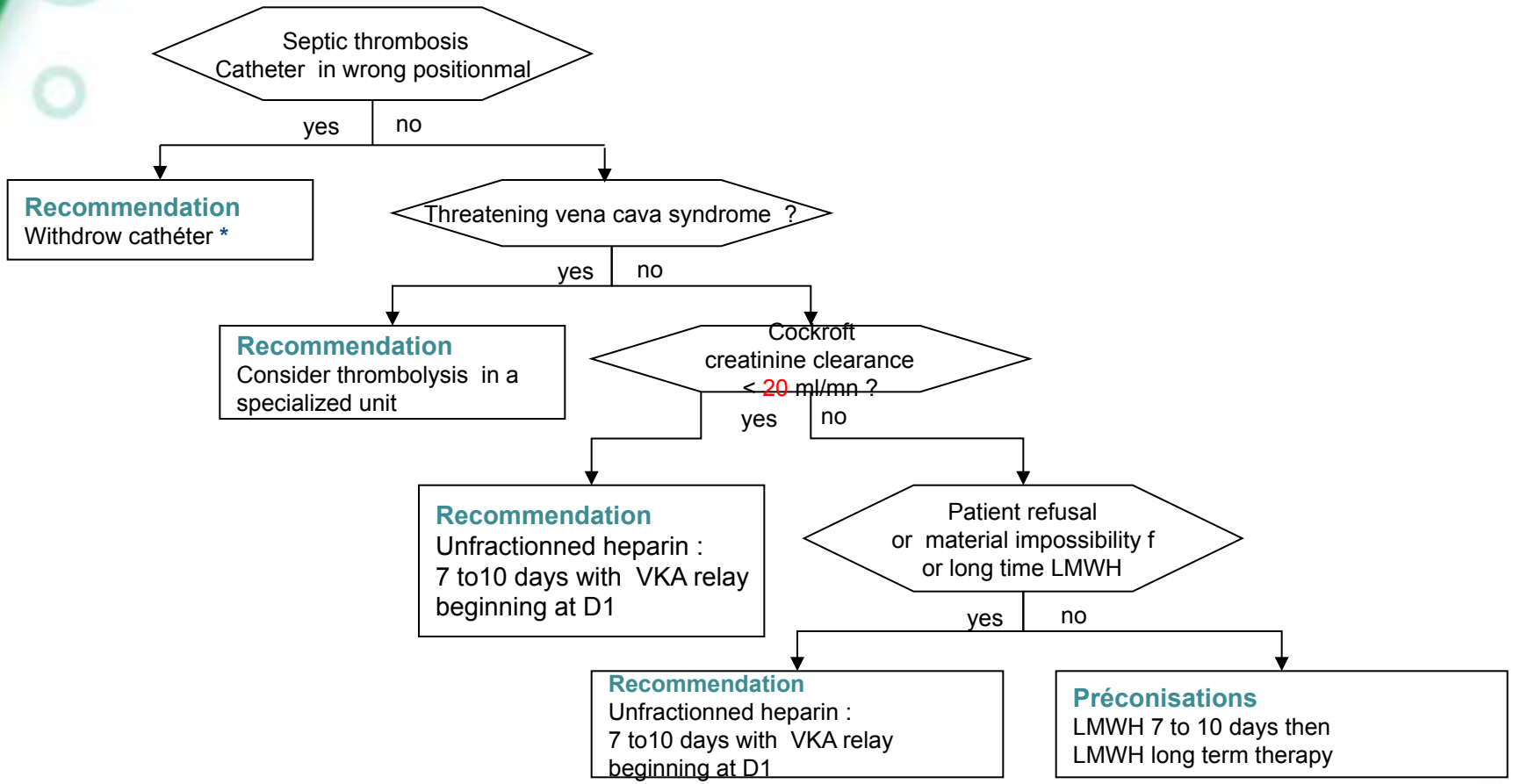
VTE recurrence under anticoagulant therapy



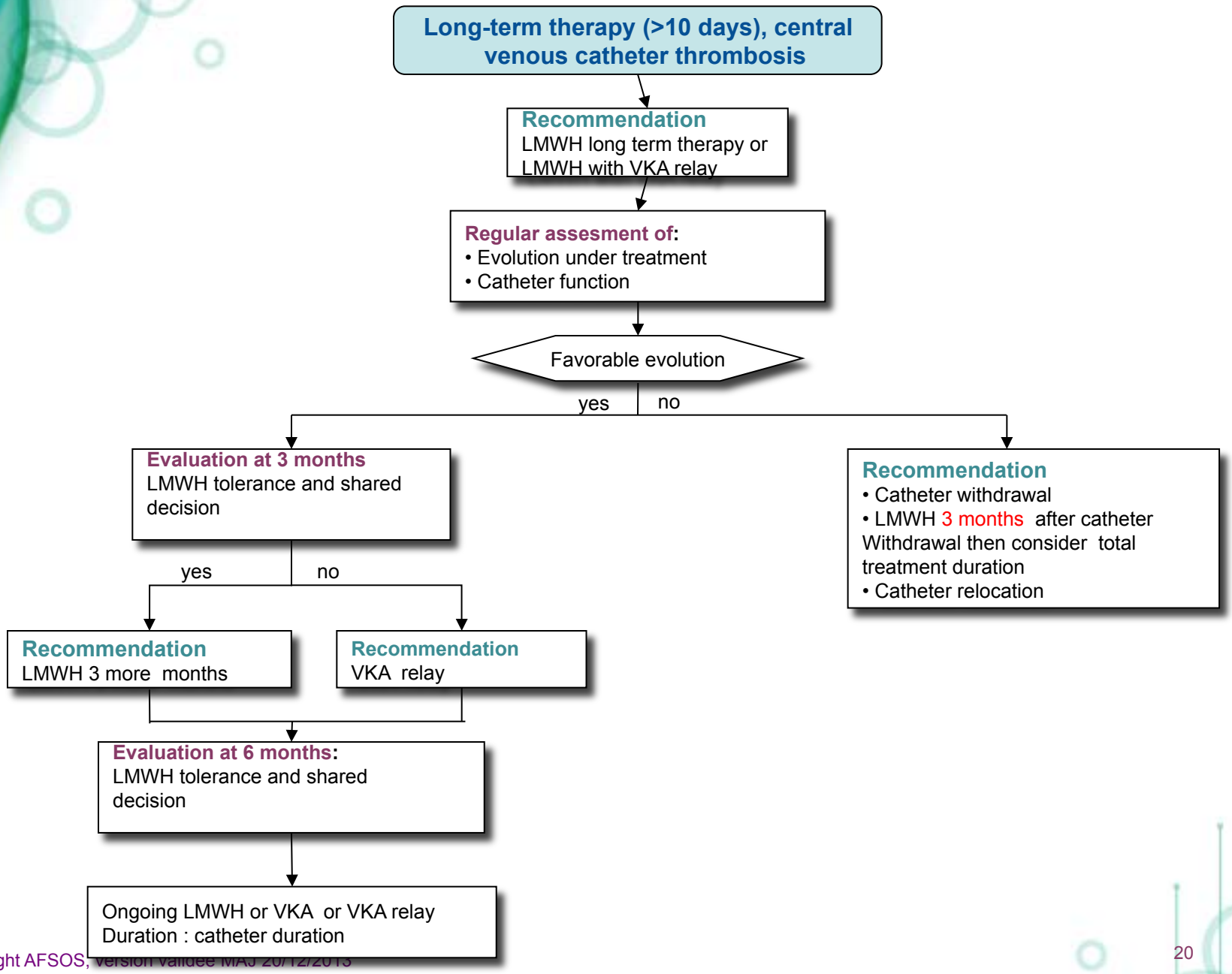
VTE treatment in case of thrombocytopenia



Initial curative treatment (<10 days), central venous catheter thrombosis



* In case of catheter withdrawal , no recommendation about the timing since the beginning of anticoagulation therapy nor on its duration (at least 6 weeks)
To be discussed , taking account of estimated survival, if catheter in wrong position



Bevacizumab and VTE risk

- Bevacizumab + chemotherapy

  – No VTE risk increase (18.5/100 PA vs 20.3/100 PA)

  Whatever of histological type, age, performans status, VTE history

  meta-analysis individual datas

- VTE during bevacizumab and chimotherapy : under curative anticoagulant therapy

  – No haemorragic risk increase

  – Low major bleeding risk (1%) and independent of bevacizumab treatment

  meta-analysis individual datas

Appendices

Frequently Asked Questions (FAQ)

Platelets monitoring under LMWH?

➢**No systematic monitoring of the platelets count** :

- In a non surgical/non traumatic context , especially under chimotherapy:
HIT brisk is < 0.1%.

HIT is an emergency situation requiring specialist advice.

Any significant decrease (about 50% of the initial) of the platelet count must give warnings, even before the value reaches the critical threshold (< 150 000 mm3).

➢**Systematic monitoring of the platelets count** during the whole treatment duration, either with prophylactic or curative treatment, **in case of** :

- Surgical context chirurgical (in the month) or traumatic context (plaster cast …) current or recent (in the 3 last months),
- non surgical / non traumatic context in case of risk factors :

History of exposure to unfractionned Heparin or LMWH in the last 6 months,

Due to the HIT risk (> 0.1%, even > 1%)

Or major comorbidity importante, due to the potential severity of HIT in these patients.

FAQ: What should we do in case of factor V Leiden mutation**?**

Studies including cancer patients with constitutional thrombophilia are rare with small nummber of patients, it is difficult to mean guidelines for VTE risk management and the in impact of constitutional thrombophilia in a cancer context

➢ Do we have to contra-indicate an antitumoral treatment ?

Inherited condition such as heterozygous factor V Leiden or FII Leiden is associated with a moderate thrombotic risk and do not contra-indicate an antitumoral treatment potentialy increasing the VTE risk. The potential benefit ot the antitumoral must outweight the thrombotic risk after discussion in a multidisciplinary board.

Two prospective trials in breast cancer dis not show an increased thrombotic incidence in patients treated with tamoxifen although they were carrying an heterozygous factor V Leiden or FII Leiden mutation. However, a more recent trial revealed that this association was significantly harmful. These conflicting datas underline the heterogeneity of the studied populations and the importance of the patients characteristics in this context.

FAQ: What should we do in case of factor V Leiden mutation**?**

Studies including cancer patients with constitutional thrombophilia are rare with small nummber of patients, it is difficult to mean guidelines for VTE risk management and the in impact of constitutional thrombophilia in a cancer context

➢ Do we have to search the mutation systematically?

Genetic features like factor V Leiden or Factor II Leiden having a variable prevalence among the general population (extraordinary risk factors), their systematic screening is unnecessary. However, it is important to check the vasculor risk profile of cancer patients (ordinary risk factors) : tobacco, overweight, familial and personnal history of VTE, cancer typedisease course, chemotherapy, surgery…

These parameters will condition the need for a wised thromboprophylaxy,either they are associated or not to this kind of genetic thrombophilia.

DOAC and cancer

DOAC : phase III trials – cancer patients - few datas, sub groups
- selected patients
- Comparator : VKA

NO INDICATION FOR DOAC IN A CANCER PATIENT WITH VTE

	EINSTEIN DVT [29]	EINSTEIN PE [30]	RE-COVER [36]	HOKUSAI
Intervention	Rivaroxaban vs. VKA	Rivaroxaban vs. VKA	Dabigatran vs. VKA	Edoxaban vs VKA
No. of patients	3449	4832	2564	8292
Study design	Open label	Open label	Double-blind	Double-blind
Treatment duration	3, 6 or 12 months	3, 6 or 12 months	6 months	12 mois
Recurrent VTE	2.1% vs. 3.0%	2.1% vs. 1.8%	2.4% vs. 2.1%	3.2% vs 3.5%
Major bleeding	0.8% vs. 1.2%	1.1% vs. 2.2%	1.6% vs. 1.9%	1.4% vs 1.6%
No. of patients with active cancer	207 (6.0%)	223 (4.6%)	121 (4.7%)	208 (2.5%)
Recurrent VTE among cancer patients	3.4% vs. 5.6%	1.8% vs. 2.8%	3.1% vs. 5.3%	3.7% vs 7.1%
Bleeding events among cancer patients	14.4% vs. 15.9%	12.3% vs. 9.3%	NR	18.3% vs 25.3%

	EINSTEIN-EXTENSION [29]	RE-MEDY [37]	AMPLIFY-EXT [34]
Intervention	Rivaroxaban vs. placebo	Dabigatran vs. warfarin	Apixaban 2.5 mg vs. Apixaban 5 mg vs. placebo
No. of patients	1196	2866	2486
Study design	Double-blind	Double-blind	Double-blind
Treatment duration	6 or 12 months	18 months	12 months
Recurrent VTE	1.3% vs. 7.1%	1.8% vs. 1.3%	3.8% vs. 4.2% vs. 11.6%
Major bleeding	0.7% vs. 0	0.9% vs. 1.8%	0.2% vs. 0.1% vs. 0.5%
No. of patients with active cancer	54 (4.5%)	119 (4.1%)	42 (1.7%)
Recurrent VTE among cancer patients	NR	3.3% vs. 1.7%	NR
Bleeding events among cancer patients	NR	NR	NR

Examples of drug interactions with DOACs*

Interaction effect*	Dabigatran P-glycoprotein	Rivaroxaban P-glycoprotein CYP3A4	Apixaban P-glycoprotein CYP3A4
Increases NOAC plasma levels†	Cyclosporine Tacrolimus Tamoxifen Lapatinib Nilotinib Sunitinib	Cyclosporine Tacrolimus Tamoxifen Lapatinib Nilotinib Sunitinib Imatinib	Cyclosporine Tacrolimus Tamoxifen Lapatinib Nilotinib Sunitinib Imatinib
Reduces NOAC plasma levels‡	Dexamethasone Doxorubicin Vinblastine	Dexamethasone Doxorubicin Vinblastine	Dexamethasone Doxorubicin Vinblastine

*: There are no datas allowing to say that these interactions are clinically relevant

Appendice 1: Score HEMORR$_2$HAGES

Letter	Clinical Characteristic	Points Awarded
H	Hepatic or renal disease	1
E	Ethanol abuse	1
M	Malignancy	1
O	Older age (>75)	1
R	Reduced platelet count or function	1
R	Rebleeding risk (ie: prior bleed)	2
H	Hypertension, uncontrolled	1
A	Anemia	1
G	Genetic factors (CYP2C9 variant)	1
E	Excessive fall risk	1
S	Stroke	1

Risk Score	Incidence of Major Bleeding (%/pt-yr)
0	1.9
1	2.5
2	5.3
3	8.4
4	10.4
>=5	12.3

Gage BF. et al. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillatiion. Am Heart J 2006; 151:713-9.

Appendice 2 : Treatments management

1. Patient treated with unfractionned heparin

Curative dose

- If IV, bolus 5000 UI IVD then 450 àto500 UI/kg/j, TCA 4 h after treatment beginning
- If SC 500 UI/kg/j 2 to 3 time per day, TCA at mid distance between two injections
- TCA between 2 to 3 times the witness or Anti-Xa 0.3 to 0.7 U/ml

Prophylactic dose

- 5000 UI SC every 8 hours in surgery
- 5000 UI SC every12 hours in medecine

Patelets count every 2 to 3 times a week

2. Patient treated with LMWH

- No anti Xa activity except patient > 100 kg our< 40 kg and creatinine clearance between 30 and 60 ml/mn (curative)
- In case of curative treatment, favour ambulatory treatment when possible
- No platelet count (Cf FAQ) in the absence of surgery, history of exposure to heparin or trauma . In the other cases, platelet count twice a week during one month or in case of symptoms evoking HIT

3. Patient treated with VKA

- In association with unfractionned heparin, LMWH or fondaparinux during at least 5 jdays in the initial setting in curative intent
- INR between2 and 3 in curative intent
- Monitoring adapted to the INR

4. Venous compression**:**

VTE prophylaxis

- During hospitalization or bedridden
- Compression stockings class 2

Post phlebitis syndroma prophylaxis

- If symptomatic lower limb VTE , not indicated for upper limb phlebitis
- Class 3, socks or stockings, depending of tolerance and capacity of dressing
- Indication to temper with estimated survival

Appendice 3 : LMWH

HBPM		Prophylactic dosage high risk	Curative dosage
DCI	**Commercial name**		
Enoxaparine	LOVENOX ®	4 000 UI/j Marketing autorisation (MA)	100 UI/kg/12h No MA in oncology
Daltéparine (AMM)	FRAGMINE®	5 000 UI/j MA	200 UI/kg/j x 1 mois then 150 UI/kg/j x 5 mois MA in oncology
Nadroparine	FRAXIPARINE® FRAXODI®	57 UI/kg/j No MA in prophylaxis in medicine	85 UI/kg/12h (0,1 ml/10kg/12h) 171 UI/kg/j (0,1 ml/10kg/12h) No MA in oncology
Tinzaparine (AMM)	INNOHEP®	3 500 à 4 500 UI/j No MA in prophylaxis in medicine	175 UI/kg/j MA in oncology

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The AGREE collaboration, version française, HAS 2002.
http://www.has-sante.fr/portail/upload/docs/application/pdf/grille.pdf

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http://www.nccn.org/professionals/physician_gls/PDF/vte.pdf

Risk assesment for venous thromboembolism (VTE) NICE
http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/@ps/documents/digitalasset/dh_113355.pdf

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Prévention et traitement des thromboses veineuses sur cathéter chez les patients atteints de cancer.
http://www.sor-cancer.fr/index.php?tg=articles&topics=70

Agence Française de Sécurité Sanitaire des Produits de Santé
Prévention et traitement de la maladie thromboembolique veineuse : www.afssaps.fr/.../5/.../RBP**ThromboembolqueVeineuse-Argu.pdf**
Modifications des recommandations de la surveillance plaquettaire: http://www.afssaps.fr/var/afssaps_site/storage/original/application/58af9a851799004cfc1317baf34a70c9.pdf
http://www.afssaps.fr/var/afssaps_site/storage/original/application/ae4209ebc36d7164d4b7c876ddeaabab.pdf

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