Paris PVT meeting 2022

Anticoagulation in patients with recent and chronic portal vein thrombosis (PVT)

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Outline

- Major/low /provoked risk factors classification
- Anticoagulation in recent portal vein thrombosis (PVT)
- Anticoagulation in chronic portal vein thrombosis (PVT)

Not referred to in this presentation:

1. Cirrhosis and other causes for obstruction than thrombosis
2. Childhood cavernoma

PVT risk factor (Major/low risk/provoked)?

- Major risk factor

Severe prothrombotic conditions:

Myeloproliferative neoplasm

NocturnalParoxysmal hemoglobinuria

Antiphospholipid syndrome

Behcet's disease

Homozygous or heterozygous composite thrombophilia gene mutations

Personal or 1st degree family history deep vein thrombosis

- Low risk factor

Isolated heterozygous G20210A factor II or G1691A factor V mutation

Isolated protein C or S deficiency

Hyperhomocysteinemia

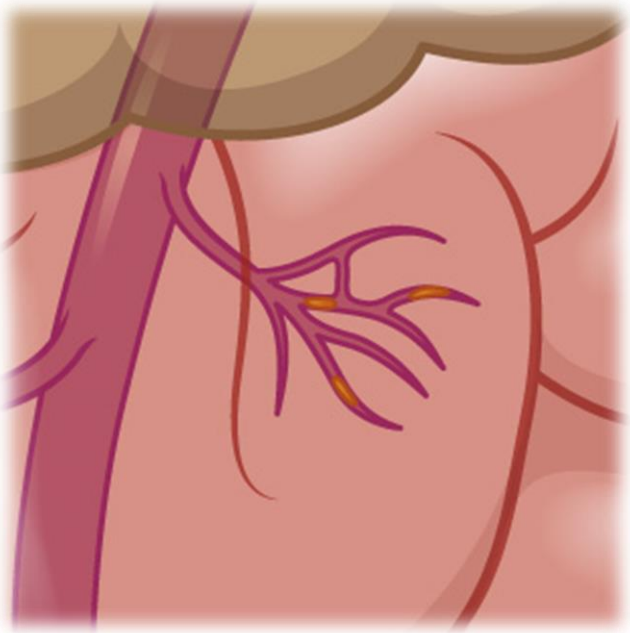
Absence of personal or 1st degree family history of venous thrombosis

- Provoked risk factor

Local cause, Oestrogen containing pill, CMV infection, covid…

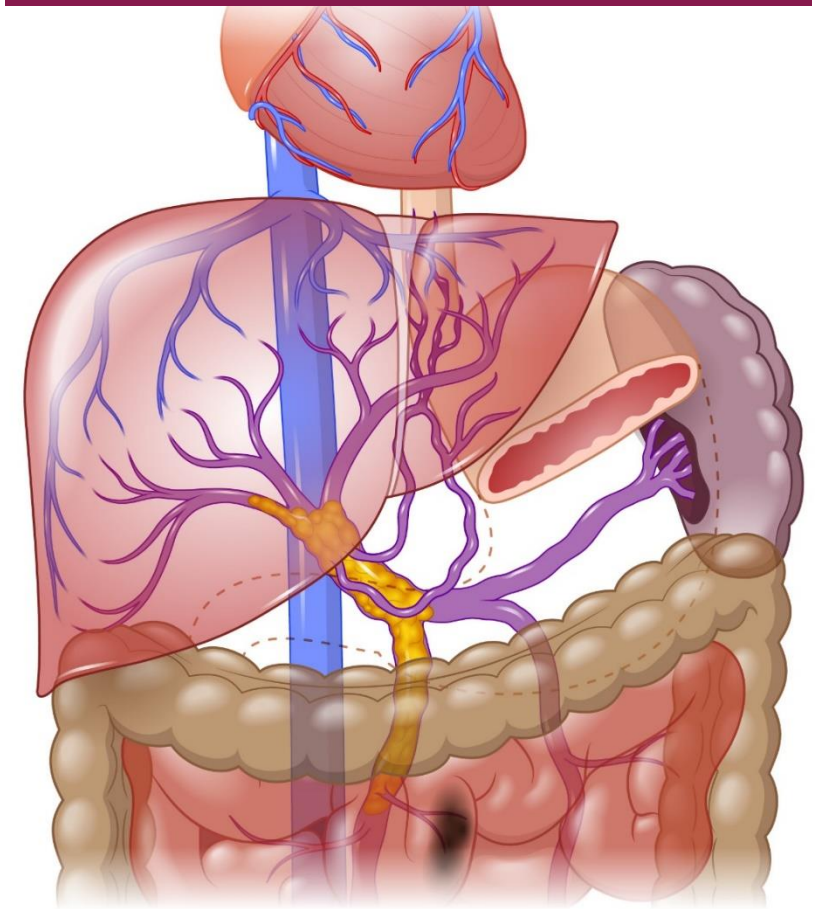
Recent PVT: Outcome after LMWH/VKA therapy

Recanalisation

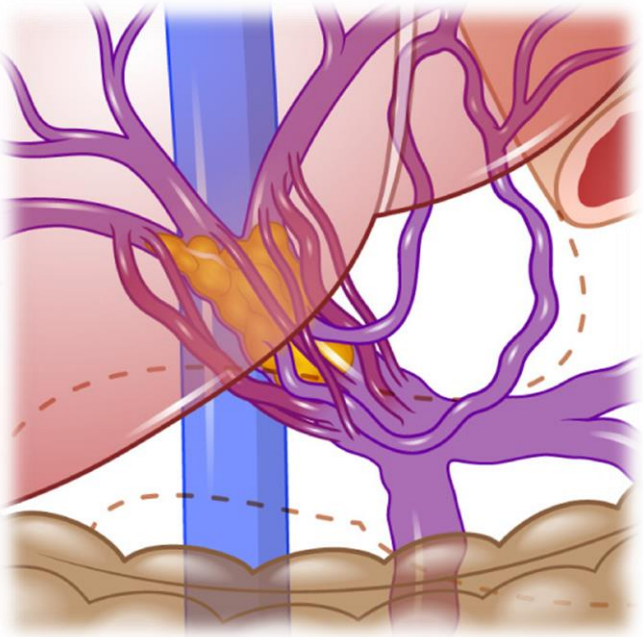


PV and branches: 38%
Mesenteric vein: 61%,
splenic vein: 54%

Small bowel resection 2-4 %

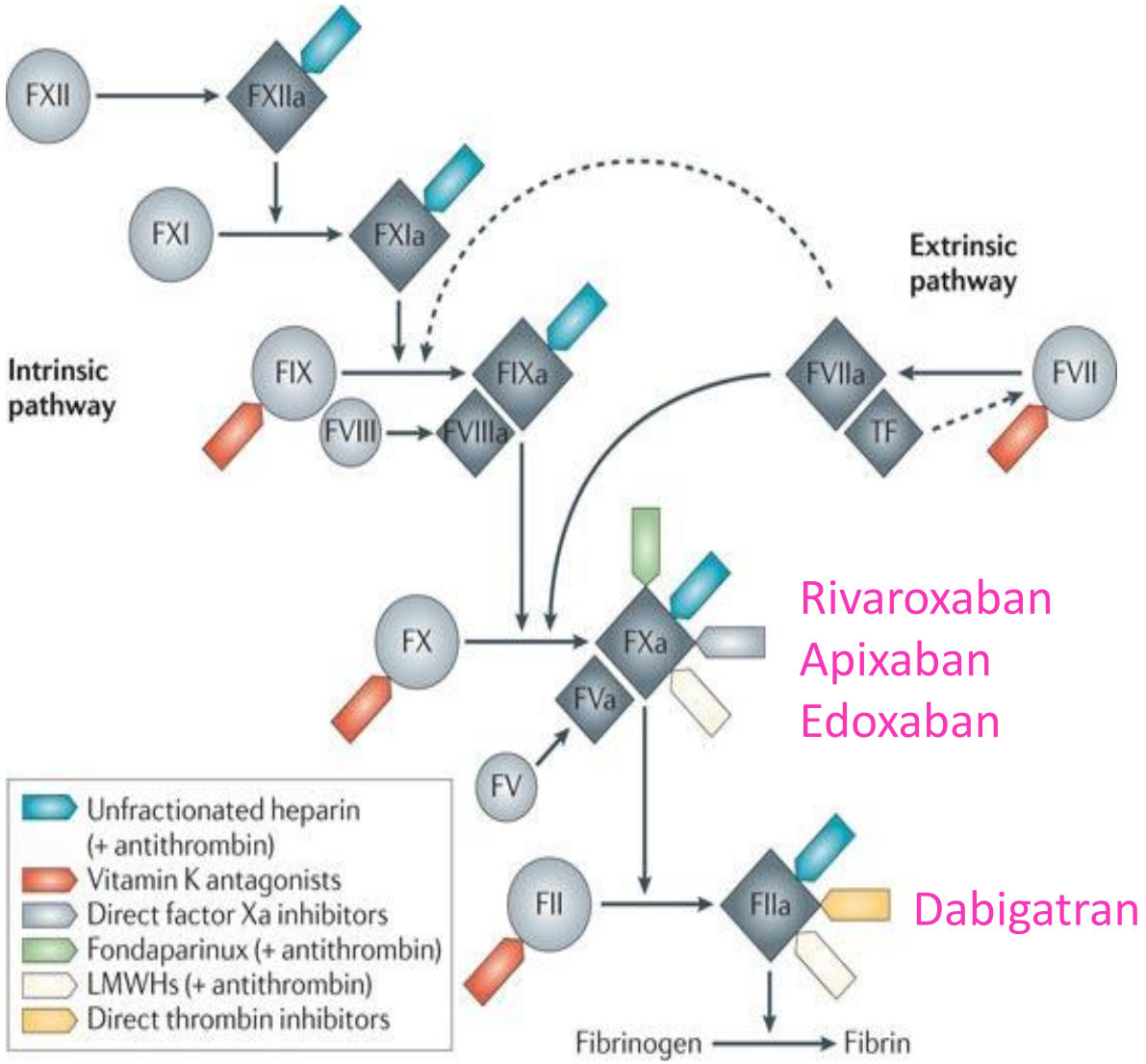


Cavernoma
40%



Plessier hepatology 2010

Direct oral anticoagulants



Rivaroxaban
Apixaban
Edoxaban

Dabigatran

	Absorption with food	Elimination ½ life
apixaban	no effect	12 h
dabigatran	no effect	12-17 h
edoxaban	6-22% more	10-14 h
rivaroxaban	40 % more	5-9 h (young) 11-13 h (elderly)

Steffel, Eur Heart J, 2018; Grzesk, Int J Mol Sci, 2021

Concerns in patients with PVT

Drug-drug interactions	via	dabigatran	apixaban	edoxaban	rivaroxaban
carvedilol/ (propranolol)	P-gp inhibitor	consider therapy modification	no action needed	consider therapy modification	no action needed
simvastatin/atorvastatin	P-gp inhibitor	consider therapy modification	no data	no data	no data
proton pump inhibitors	decreased GI absorption	-30%	no relevant effect	no relevant effect	no relevant effect

- DOACs should be used with caution in patients with creatinine clearance below 30 mL/min or liver failure
- DOACS should not be used in “triple positive” anti-phospholipid syndrome and pregnancy

Burnett, J Thromb Thrombolysis, 2016; Wessler, JACC, 2013; Steffel, Eur Heart J, 2018; Lexicomp Drug Interactions, 2018; Chen, JAHA, 2020

Doacs in recent non cirrhotic portal vein thrombosis

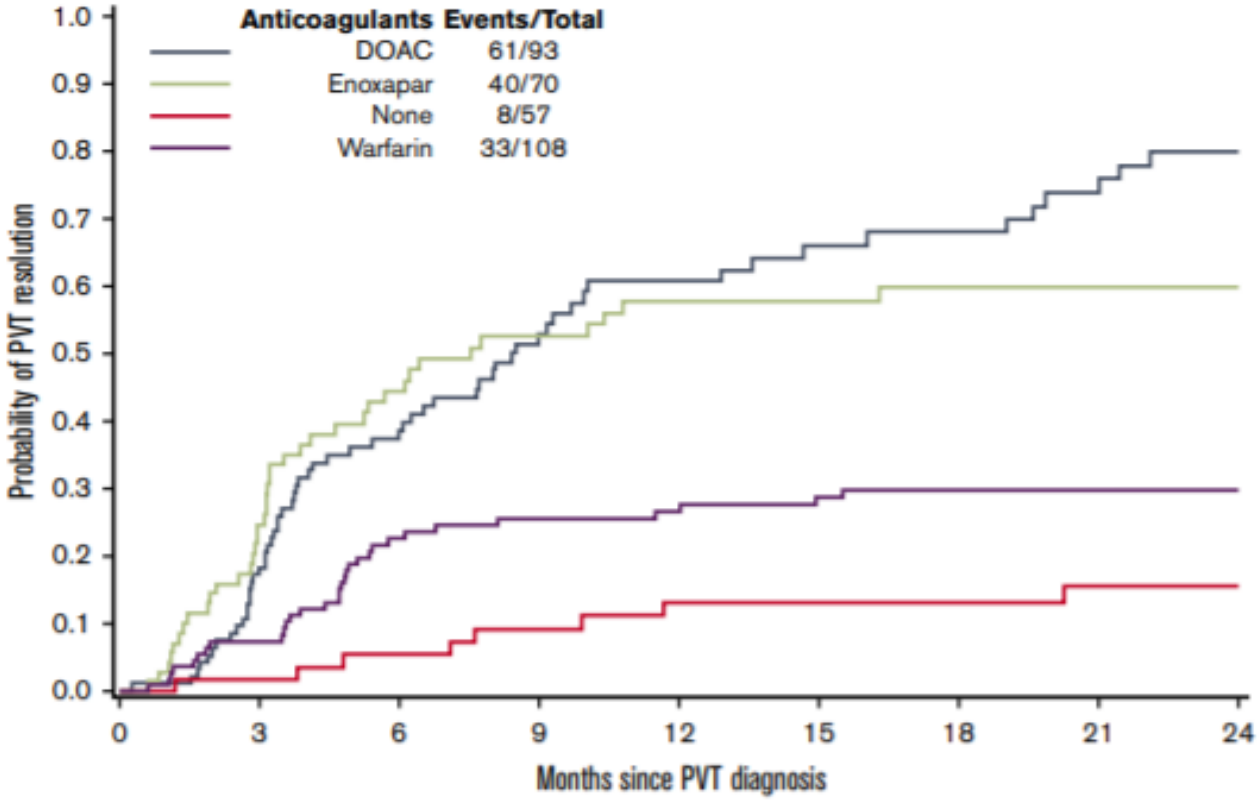
- No randomised studies
- All retrospective
- Most cirrhosis & non cirrhotic

Predisposing factors for PVT	N=330
Intraabdominal surgery	103 (32)*
Inflammatory bowel disease	63 (19)
Intraabdominal infection	48 (15)*
Non-HCC malignancy	42 (13)
JAK2 V617F mutation	37 (11)†
Pancreatitis	21 (6)*
Estrogen-containing OCP use	14 (4)
Pregnancy	5 (2)*
Other	8 (2)
2 or more factors	70 (21)
None	90 (27)

Scheiner B, Stammet PR, Pokorny S, et al. *Wien Klin Wochenschr.* 2018 ; 130 : 446–455
Naymagon L, Tremblay D, Zubizarreta N, Moshier E, Schiano T, Mascarenhas J. *Blood advances* 2019 ; 134 :1154
Surgery. 2021 May;169(5):1175-1181; Inflamm Bowel Dis. 2021; De Gottardi

Doacs in non cirrhotic (acute) portal vein thrombosis

Probability of complete radiographic resolution



- DOACS = LMWH and DOACS > Warfarin
- Each individual DOAC >warfarin
- In warfarin group: 62% of international normalized ratio assessments were in therapeutic range

lower risk for major bleeding with DOACs vs warfarin p=0,03

Naymagon L, *Blood advances* 2019 ; 134 :1154

Risk factors for poor outcome or absence of recanalisation

- Anticoagulation initiation delay or Warfarin derivatives
- Ascites
- Extension of thrombosis (to splenic vein or occlusion of second order radicles of the superior mesenteric vein)
- Type 2 diabetes, myeloproliferative disorder

bowel infarction suspicion / low likelihood of anticoagulation recanalisation

anticipate anticoagulation failure, mutidisciplinary approach early recanalisation?

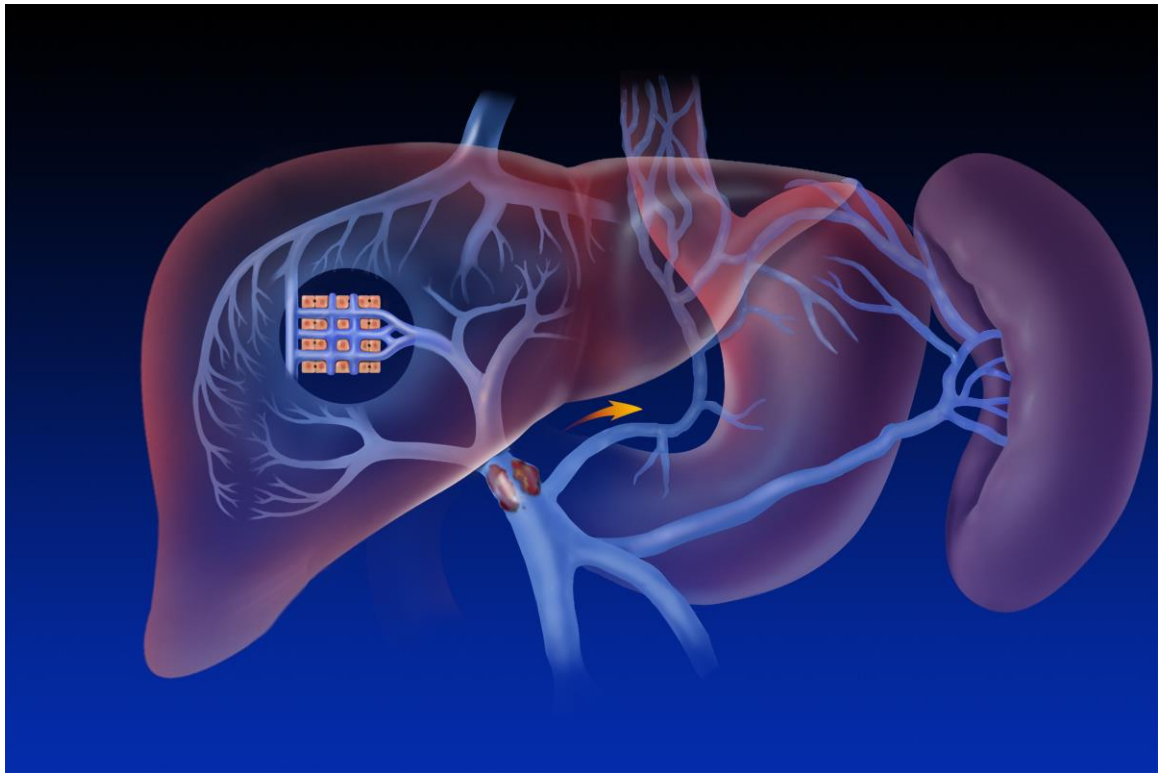
Turnes CGH 2008, Plessier Hepatology 2010, Elkrief liver int 2014, Naymagon blood advances 2019, Benmassaoud A P T2019

Specificities of anticoagulation in the setting of recent portal vein thrombosis

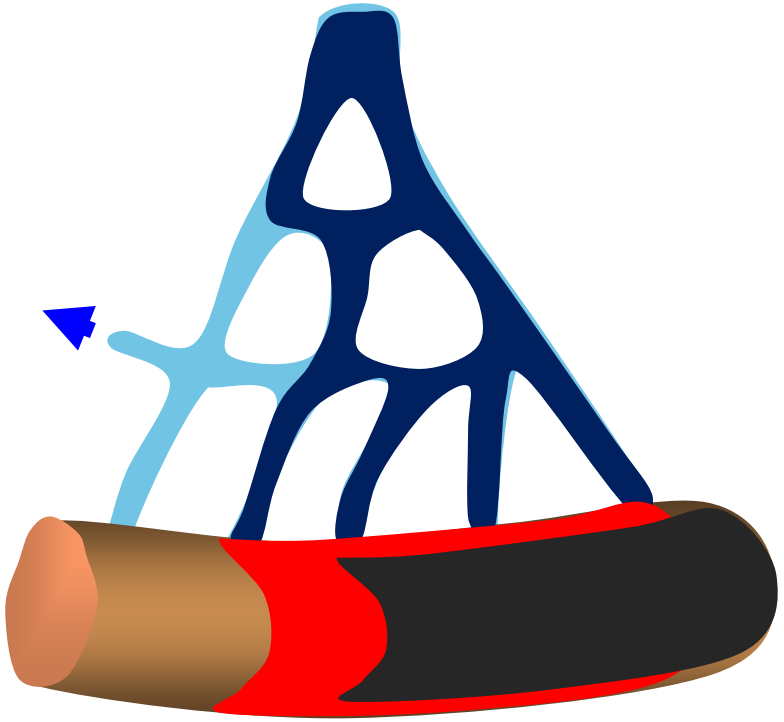
- Low Molecular Weight Heparin are widely accepted. Anticoagulation should be started at therapeutic dosage immediately at diagnosis
- High Prevalence of Heparin Induced Thrombocytopenia (especially in patients with Myeloproliferative neoplasm)
- As a primary treatment option for recent portal vein thrombosis in the absence of cirrhosis, start with low molecular weight heparin and switch to vitamin K antagonists when possible(B.1)
- DOACS can be considered as primary option in selected cases in the absence of so-called “triple positive” anti-phospholipid syndrome, although data are limited

De Franchis Baveno VII, Randi et al. Acta Hematol 2010

Chronic portal vein thrombosis



Variceal bleeding



Thrombosis recurrence

Rational for permanent anticoagulation in major risk thrombotic factors

Recurrent thrombosis and prognostic factors for recurrence

SVT cohorts

Recurrent thrombosis incidence per 100 patient-years	Ageno N =604	Condat N=136
Total	7.3	5.5
With anticoagulation	5.6	3.8
Anticoagulation discontinuation	10.5	6.3

Ageno: Male sex, solid cancer, myeloproliferative neoplasms, and unprovoked SVT
Condat: Thrombophilia and anticoagulation

MPN cohorts

- Recurrent thrombosis incidence rate of 4.2 per 100 pt-years
  - VKA :3.9 per 100 pt-years, whereas in the small fraction (15%) not receiving VKA :7.2 per 100 pt-years
- Risk factor for TIPS obstruction in BCS

Ageno JAMAInternMed.2015; Greenfield Thrombosis 2018
De Stefano Blood Cancer Journal 2016 Hayek Radiology 2017

Recurrent thrombosis in unprovoked PVT

	Myeloproliferative Neoplasm (n = 49)	Unprovoked SVT (n = 163)	Transient Risk Factors[b] (n = 105)
Major bleeding events	3 Events; 3.6 per 100 patient-years (1.1-11.1)	5 Events; 1.7 per 100 patient-years (0.7-4.2)	1 Event; 0.5 per 100 patient-year (0.1-3.7)
Thrombotic events	5 Events; 5.9 per 100 patient-year (2.5-14.3)	18 Events; 6.3 per 100 patient-year (4.0-10.0)	6 Events; 3.2 per 100 patient-year (1.4-7.0)
Mortality	3 Events; 3.4 per 100 patient-year (1.1-10.4)	7 Events; 2.3 per 100 patient-years (1.1-4.8)	5 Events; 2.5 per 100 patient-years (1.1-6.1)

JAMA Intern Med. 2015;175(9):1474-1480. doi:10.1001/jamainternmed.2015.3184

NGS « high molecular risk » in idiopathic PVT

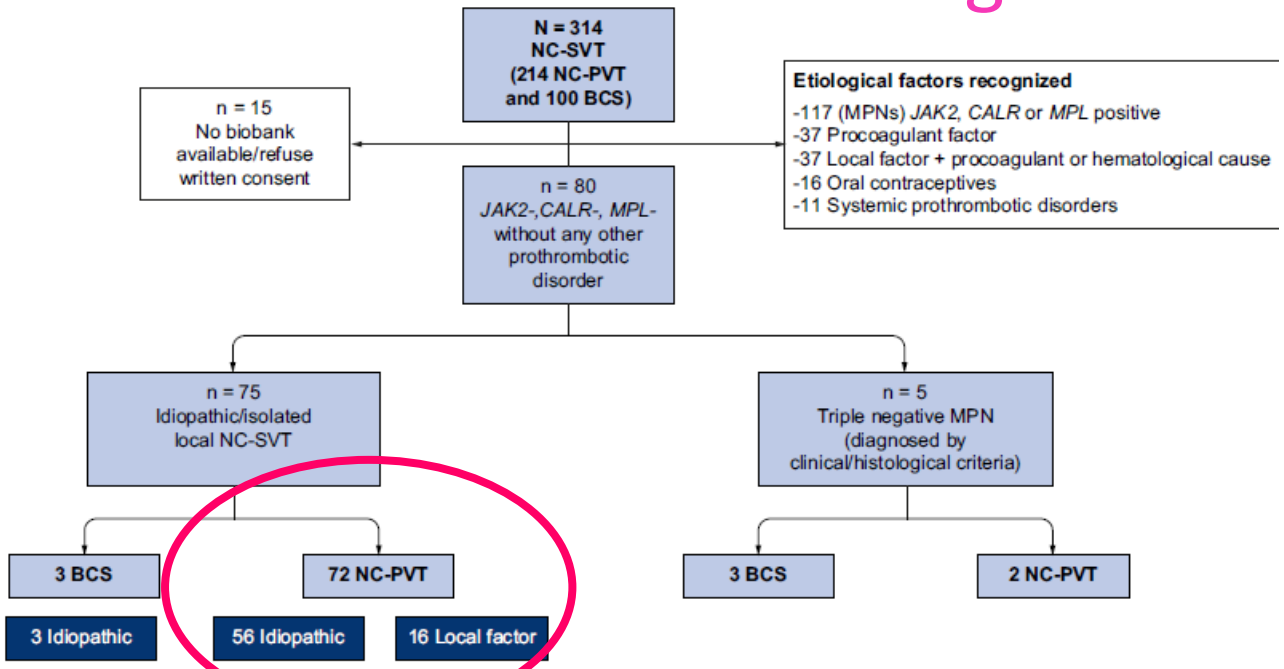
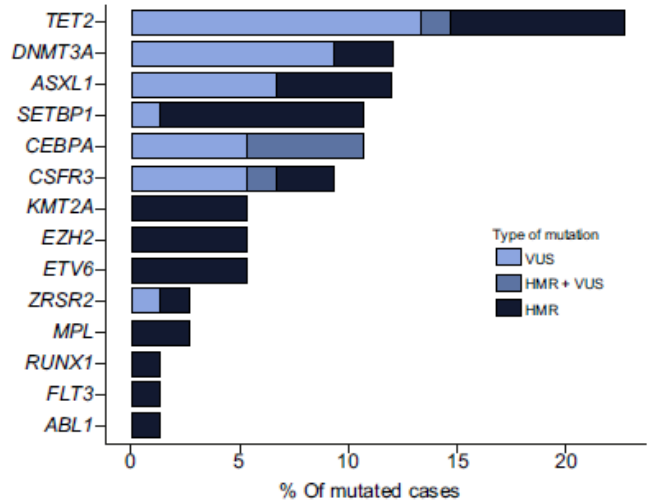
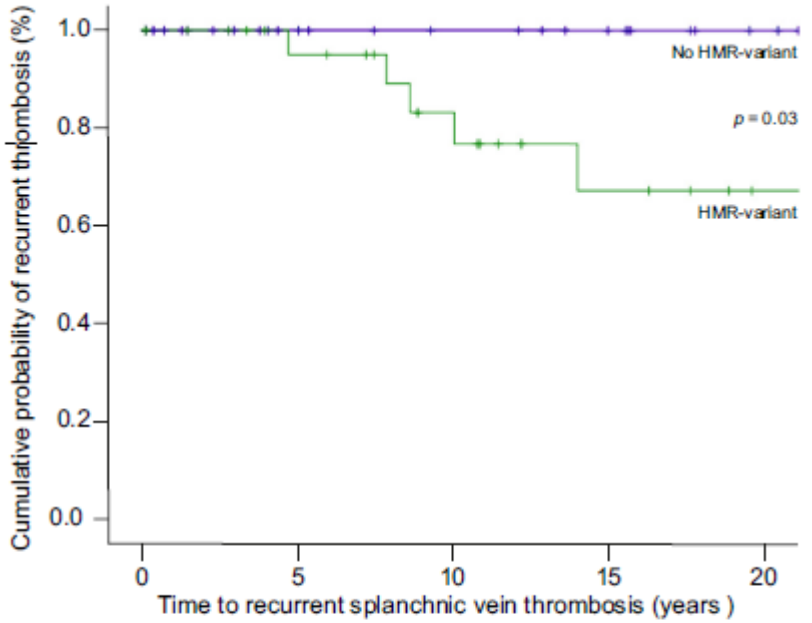


Fig. 1. Patient flow chart. BCS, Budd-Chiari syndrome; *CALR*, calreticulin gene; *JAK2*, Janus kinase 2 gene; *MPL*, thrombopoietin gene; MPN, myeloprc neoplasm; NC-PVT, non-cirrhotic portal vein thrombosis; NC-SVT, non-cirrhotic splanchnic vein thrombosis.



2. Mutation frequency of all variants detected by NGS. HMR, gh-molecular-risk variant; NGS, next-generation sequencing; VUS, variant of known significance.



Patients at risk					
HMR-variant	26	22	16	11	6
No-HMR	36	23	19	15	8

Fig. 3. Cumulative incidence of recurrent splanchnic vein thrombosis in 62 patients with chronic portal vein thrombosis of idiopathic/local aetiology not receiving long-term anticoagulation comparing those with and without HMR variants. The probability of recurrent thrombosis as a function of time was estimated using the Kaplan-Meier method. HMR, high-molecular-risk variant; VUS, variant of unknown significance.

Magaz J Hepatol 2021

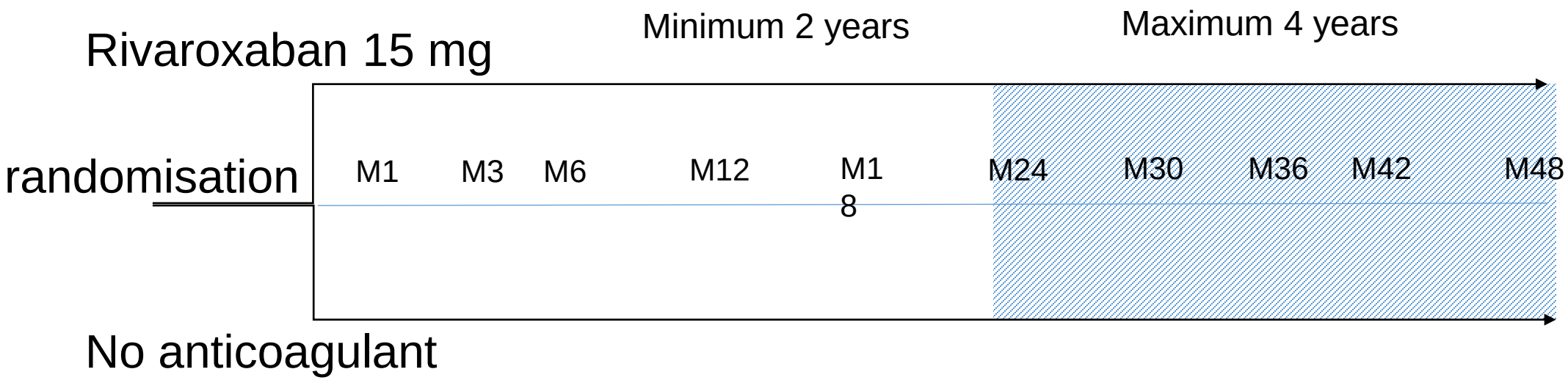
Low risk/idiopathic or provoked factor for thrombosis

Permanent anticoagulation?

DOACS in this indication?

Riport study : methods

- Randomized, open-blinded controlled trial between September 16, 2015 and January 30, 2020



Stratification according to anticoagulant therapy at inclusion and center
Independent committee blinded to treatment arm assessed recurrent thrombotic event

Primary end-point: thromboembolic event in any venous territory, or death

Plessier, NEJM evidence 2022

Methods

- **Inclusion criteria**:
  - portal cavernoma or
  - recent portal vein thrombosis >6 months,

  without major-risk factors for recurrent thrombosis

- **Exclusion criteria**:
  - myeloproliferative diseases
  - antiphospholipid syndrome or
  - homozygous or composite heterozygous G20210A factor II and G1691A factor V mutations
  - personal or 1st degree unprovoked family history of venous thrombosis
  - past mesenteric infarction

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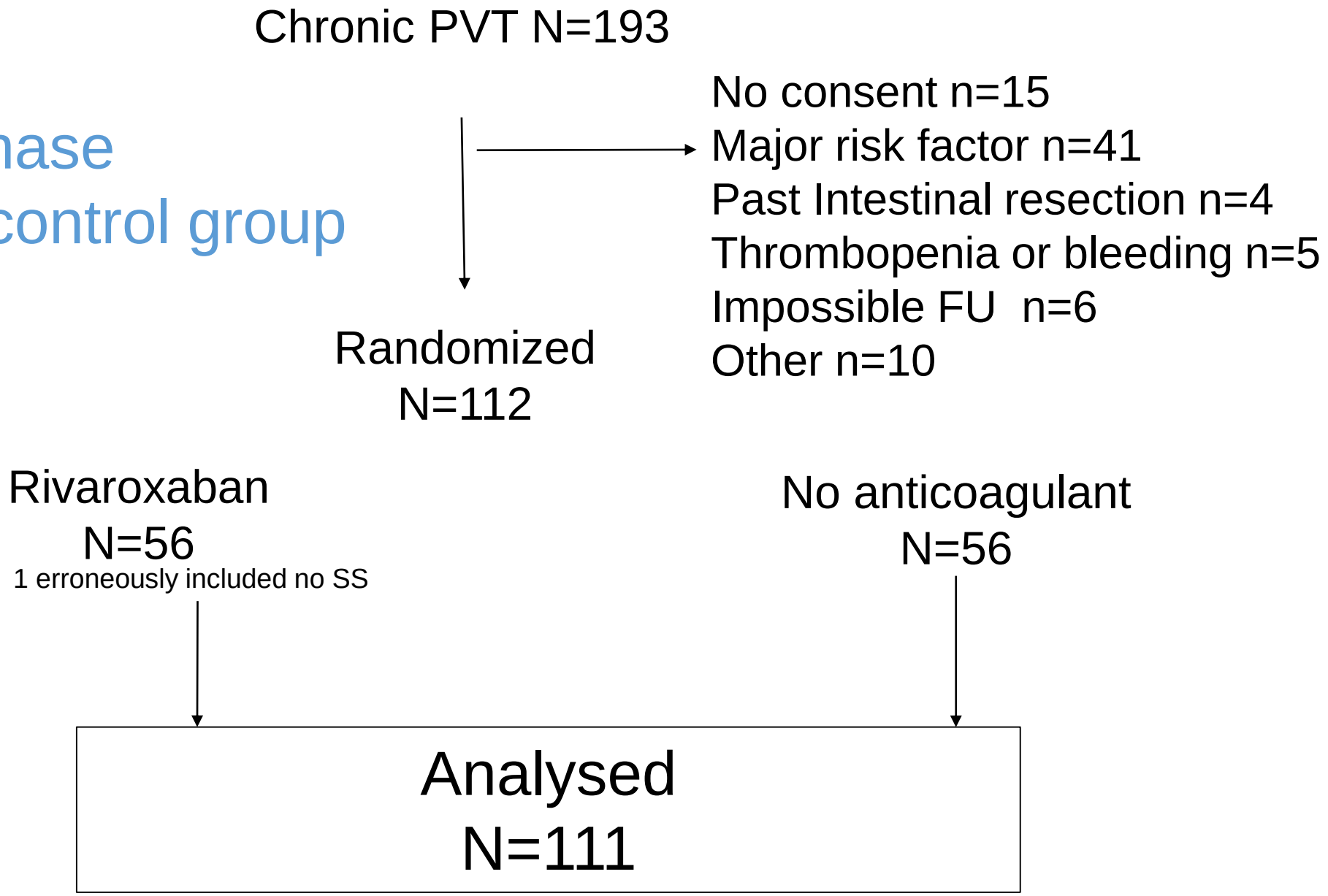
Period 1
randomisation phase
Rivaroxaban vs control group



Characteristics of patients at inclusion

	Rivaroxaban (N=55)	No anticoagulation (N=56)	p-value
Age	50.5 [41.6-60.8]	48.1 [42.3-61.5]	0.92
Male gender	56%	59%	0.78
Ongoing anticoagulation at inclusion	71%	77%	0.48
Thrombophilia (low risk)	60%	42%	0.08
Esophageal varices	33%	25%	0.34
Portal cavernoma	76%	64%	0.16
Length of clot			0.65
Intrahepatic	22%	29%	
Intrahepatic and extrahepatic	67%	58%	

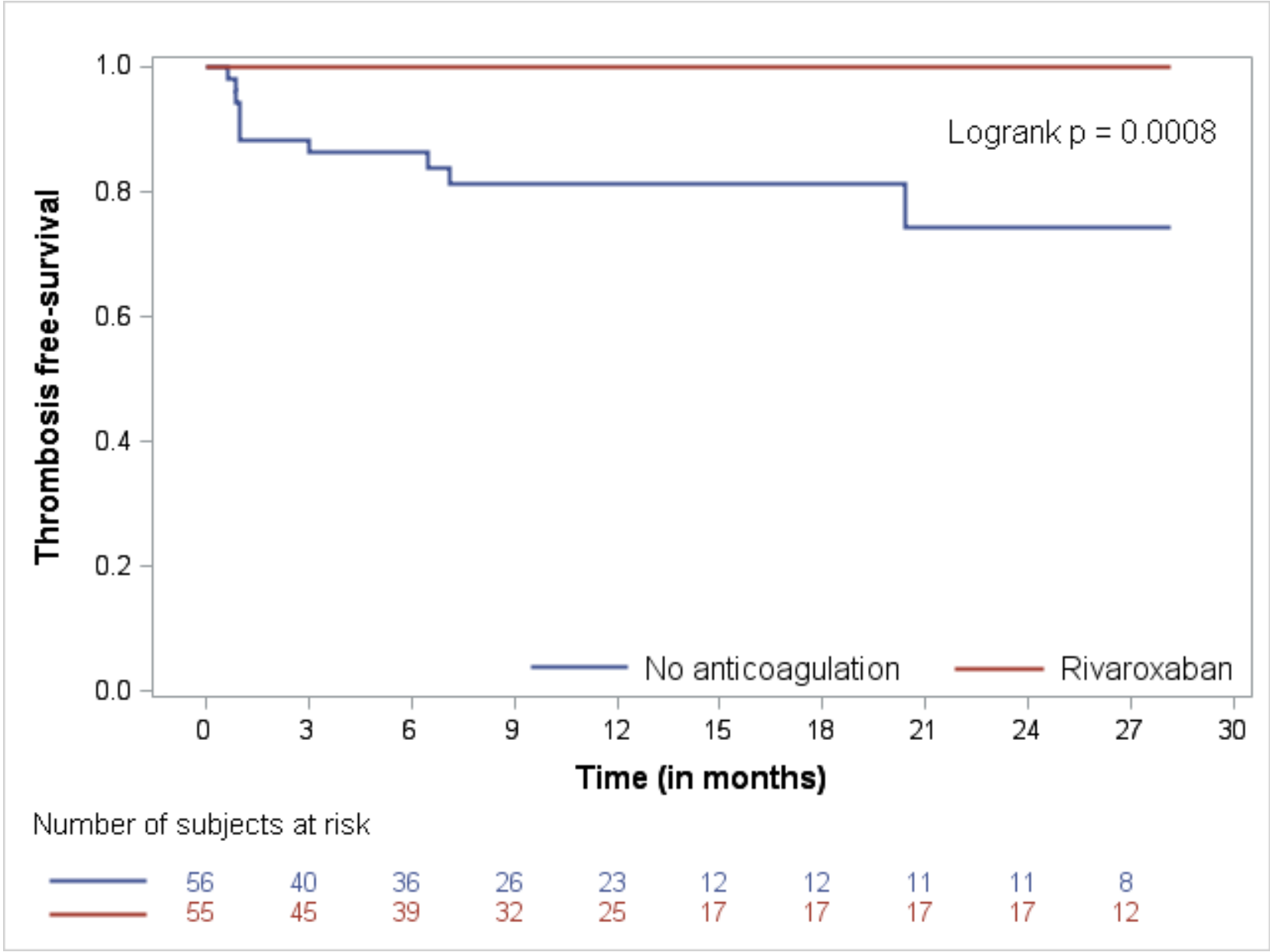
Thrombosis-free survival

Rivaroxaban : 0 event
Incidence rate 0/100 patient-years

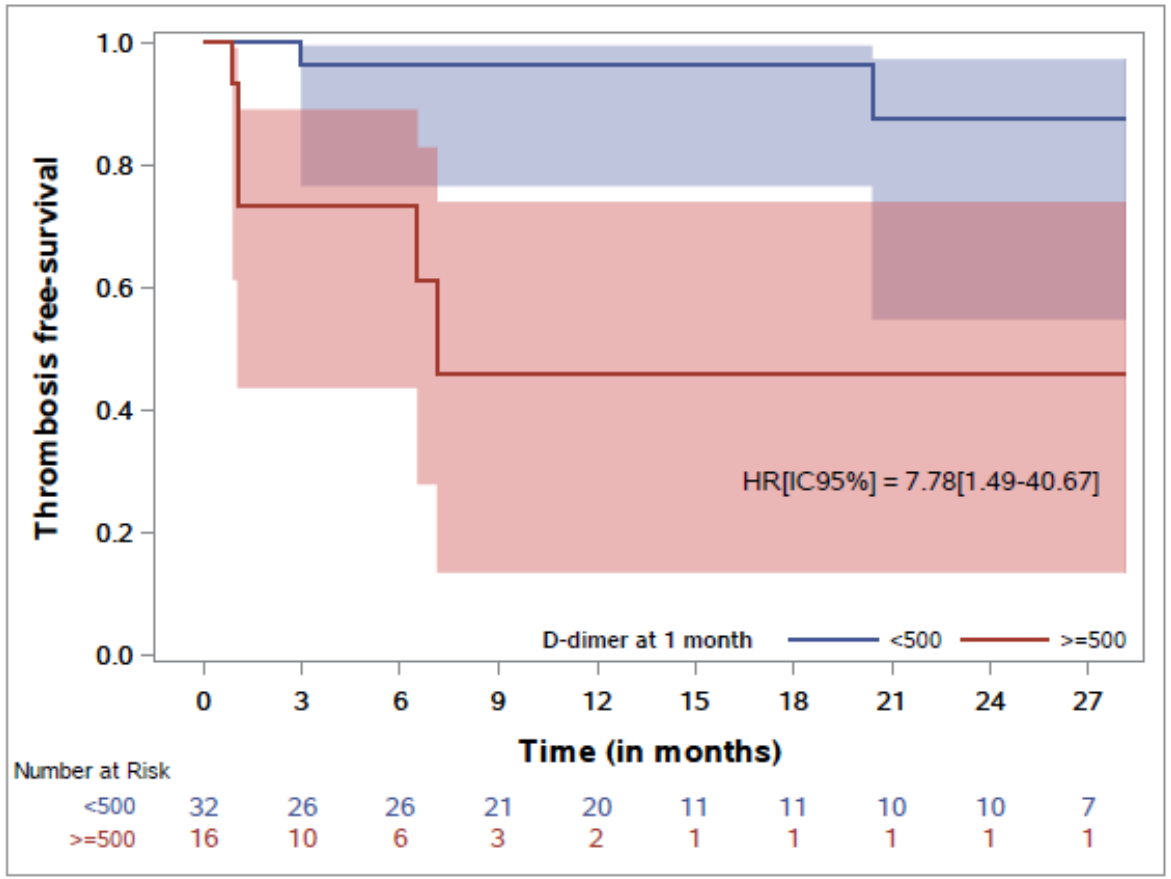
No anticoagulation : 10 events.
Incidence rate 19.7/100 patient-years
[7.5 – 31.9]

- Phlebitis 3
- pulmonary embolisms 3
- splanchnic thrombosis 4

Median FU 11.8 months (95% IC [8.8-13.2]



Thrombosis free survival according to D-dimer level in no-anticoagulation group



- D-dimer M 1> 500 ng/mL predictive positive value (PPV) 37.5 %
- D-dimer M1 < 500 ng/mL negative predictive value (NPV) 93.5%

D-Dimer > 500 ng/mL associated to thrombosis recurrence (HR=7.78 [1.49-40.67])

Factors associated with thrombosis among patients randomized in the non-treated group

	Thrombosis (n=10)	No thrombosis (n=46)	HR [IC 95%]
Age (years)	44.6 [36.2-50.7]	49.3 [43.0-64.0]	0.97 [0.92-1.02]
IMC>30 n (%)	3 (30)	13 (28)	1.00 [0.25-3.98]
Thrombophilia			
Protein S deficiency* n (%)	1 (10)	5 (11)	0.60 [0.07-4.84]
Protein C deficiency<70% n (%)	1 (10)	7 (15)	0.50 [0.06-4.00]
Hyperhomocysteinemia n (%)	1 (11)	11 (28)	0.48 [0.06-3.97]
local causes/estroprogestative within 3 months of initial thrombosis n (%)	0	19 (41)	-
Repermeabilization	0	6 (13)	-
D-dimers at 1 month ≥500 ng/mL n (%)	6 (75)	10 (25)	7.78 [1.49-40.67]
Factor VIII at 1 month >150% n (%)	4 (50)	16 (40)	1.47 [0.32-6.71]

Rivaroxaban
N=55

No anticoagulant
N=56

Period 2:open-label follow-up
Switch to anticoagulation

Anticoagulant N=99

No anticoagulant N=12

Rivaroxaban N=78

Other anticoagulant N=21

Complications

Median follow-up: 30.3 months [29.8-35.9]

	N events	PY	Incidence rate 100 PY[IC 95%]	Incidence RR[IC 95%]	p
Severe bleeding					
No anticoagulant	1	81.26	1.23 [0.00 – 3.64]	1	-
DOACS	2	196.35	1.02 [0.00 – 2.43]	0.83 [0.07 – 9.13]	0.8773
VKA or heparins	0	36.74	0	-	-
Minor bleeding					
No anticoagulant	4	81.26	4.92 [0.10 – 9.75]	1	-
DOACS	47	196.35	23.94 [17.09 – 30.78]	4.86 [1.75 – 13.50]	0.0024
VKA or heparins	6	36.74	16.33 [3.26 – 29.39]	3.32 [0.94 – 11.76]	0.0632
Variceal bleeding					
No anticoagulant	1	81.26	1.23 [0.00 – 3.64]	1	-
DOACS	3	196.35	1.53 [0.00 – 3.26]	1.24 [0.13 – 11.94]	0.8513
VKA or heparins	1	36.74	2.72 [0.00 – 8.06]	2.21 [0.14 – 35.36]	0.5746
Other complications					
No anticoagulant	1	81.26	1.23 [0.00 – 3.64]	1	-
DOACS	6	196.35	3.06 [0.61 – 5.50]	2.48 [0.30 – 20.63]	0.3997
VKA or heparins	0	36.74	0	-	-

Conclusion Riport study

- In patients with long-standing PVT without Major-risk factor for thrombosis, rivaroxaban reduces the incidence of recurrent venous thrombosis without increasing the occurrence of severe bleeding.

Plessier, NEJM evidence 2022

Anticoagulation when?

1. Recent PVT
2. Acute on chronic PV thrombosis

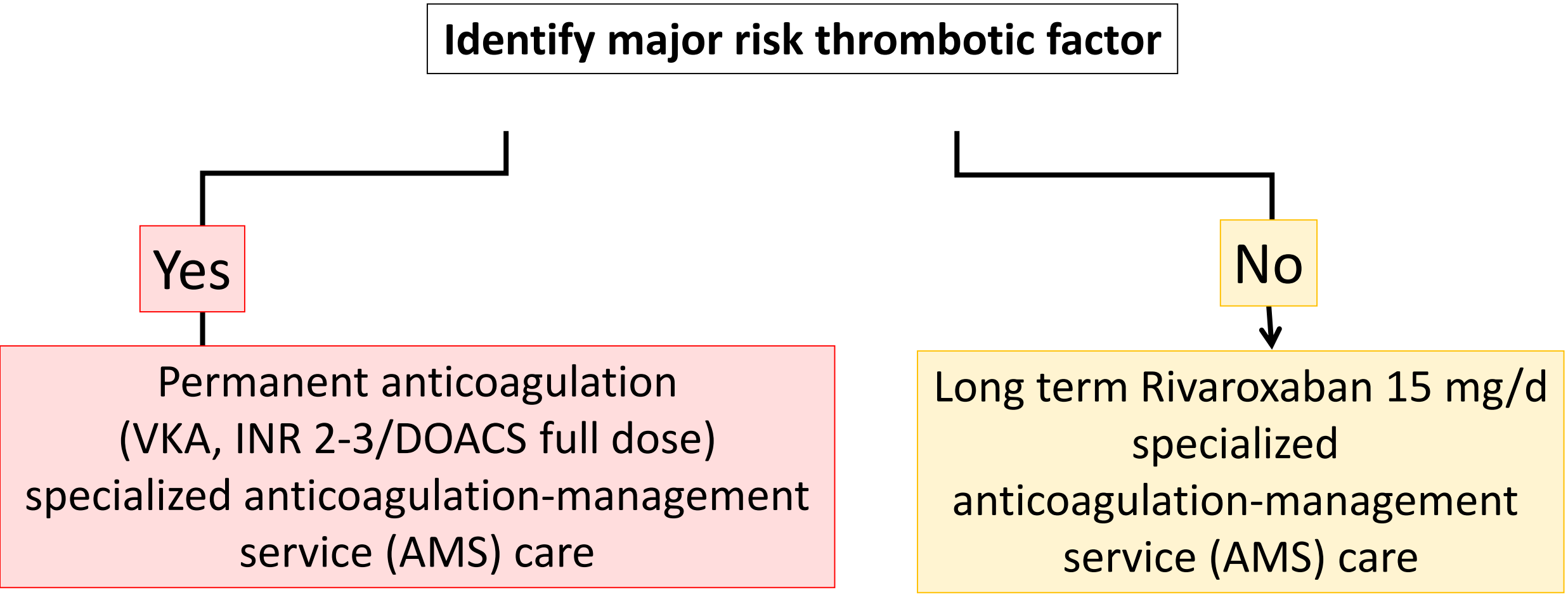
3. Chronic PVT diagnosed for PHT complication or incidentally

Urgent anticoagulation / Identification and treatment of thrombosis risk factor

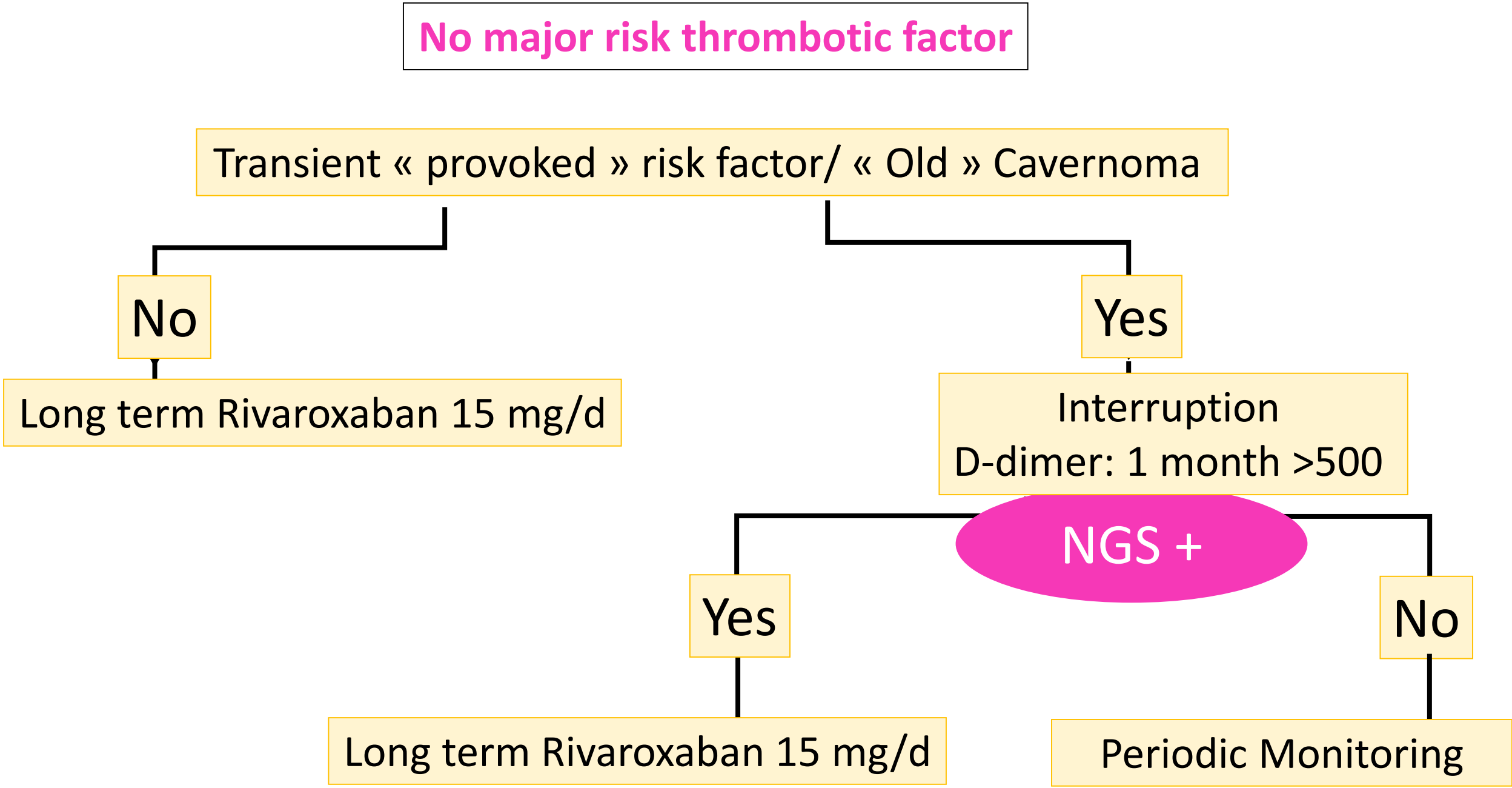
No urgent anticoagulation needed, identification and treatment of thrombosis risk factor

Time for RCP discussion

Anticoagulation in portal vein cavernoma

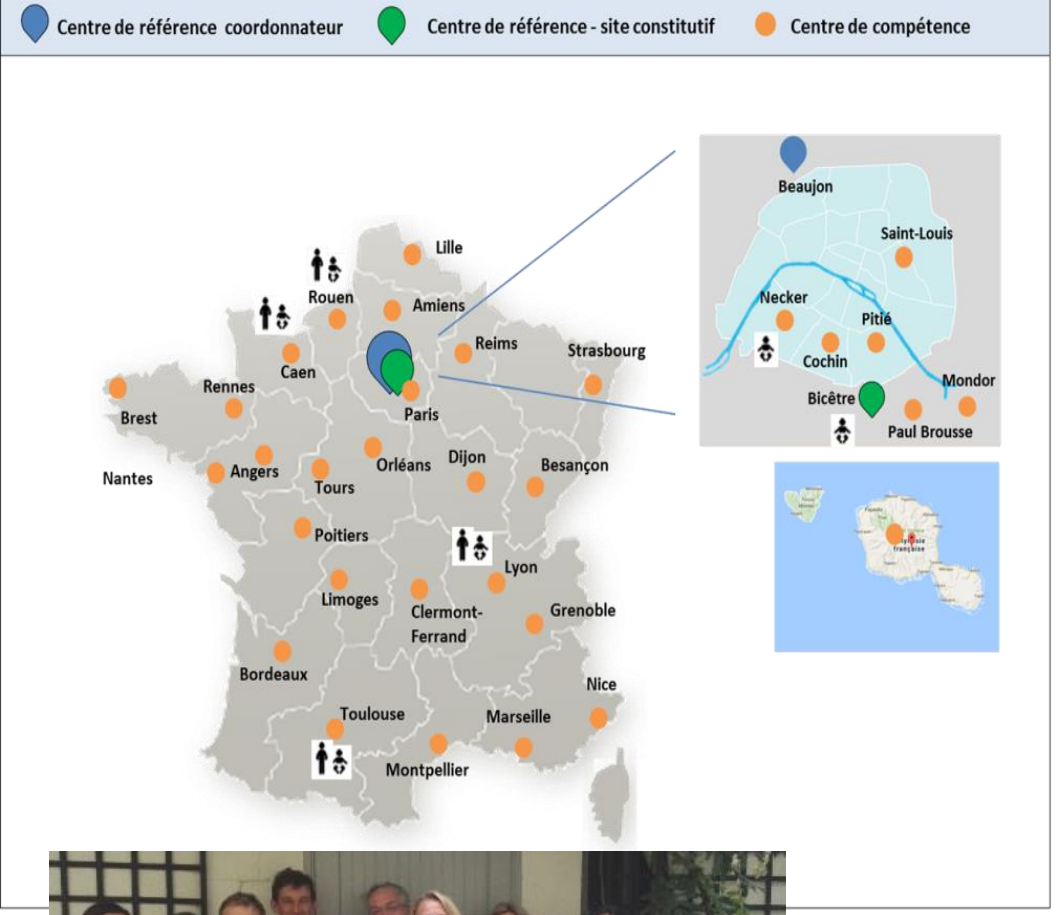


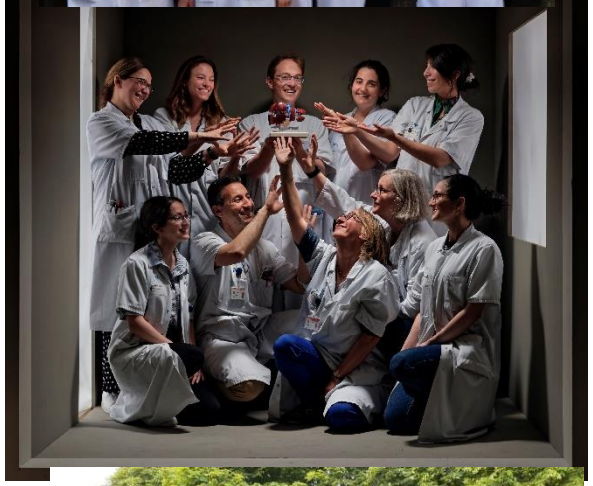
Treatment reassessment at periodic intervals


No major risk thrombotic factor
Transient « provoked » risk factor/ « Old » Cavernoma
No
Long term Rivaroxaban 15 mg/d
Yes
Interruption
D-dimer: 1 month >500
NGS +
Yes
Long term Rivaroxaban 15 mg/d
No
Periodic Monitoring

Anticoagulation in PVT

- DOACS can be considered as primary option in the absence of contra indication
- Associated treatment of the cause is needed
- In patients not responding to anticoagulation, radiological intervention, should be considered with a multidisciplinary approach in referral centers
- In patients with chronic PVT, including those with incomplete resolution of recent PVT at 6 months, discuss long term anticoagulation.
  - ✓ Interruption may be considered in transient provoked PVT, especially in NGS negative PVT ? D-dimers < 500 ng/mL one month after discontinuation may be used to predict a low risk of recurrence. Studies needed
- Adequate portal hypertensive bleeding prophylaxis initiated
- Patient's education programs and patient's association support





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