



Troubles de l'hémostase dans la cirrhose : évaluation, prévention et traitement des hémorragies post-procédure invasive

Pierre-Emmanuel RAUTOU

Inserm U1149, Centre de recherche sur l'inflammation, Paris

Service d'hépatologie, Hôpital Beaujon, Clichy, France

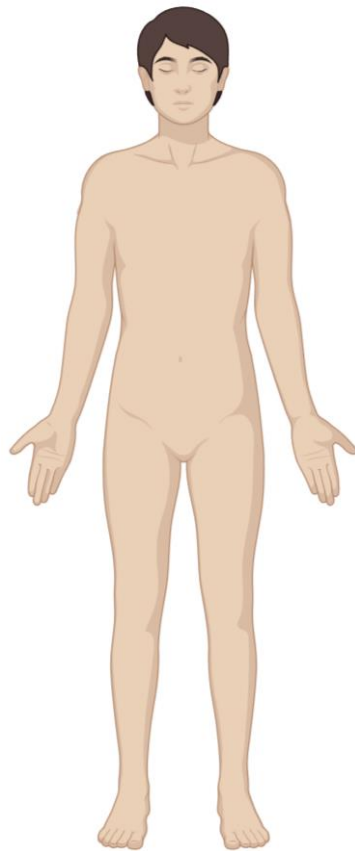
pierre-emmanuel.rautou@inserm.fr

Conflicts of interest

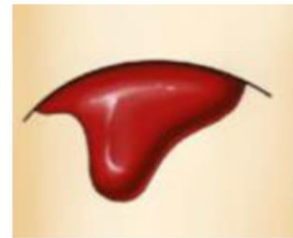
- I do not have a financial relationship relevant to that presentation
- I am not discussing off-label investigative use of a drug/device/product

Bleeding in patients with cirrhosis

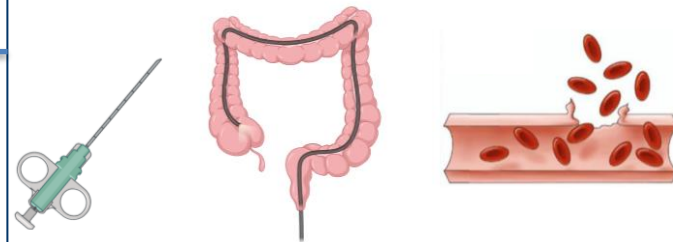
Portal hypertension



Haemostasis related



Post-procedure



Invasive procedures in patients with cirrhosis

- Coagulation changes in patients with cirrhosis
- Management of invasive procedures in cirrhosis
- Management of anticoagulants and antiplatelet agents

Coagulation in cirrhosis

Primary hemostasis:

platelet aggregation

Coagulation:

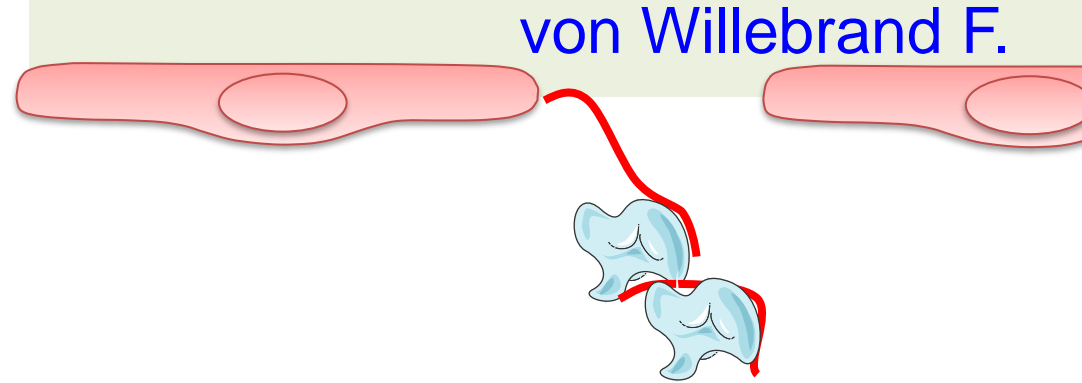
fibrin formation

Fibrinolysis:

fibrin lysis

Coagulation in cirrhosis

Primary hemostasis:
platelet aggregation



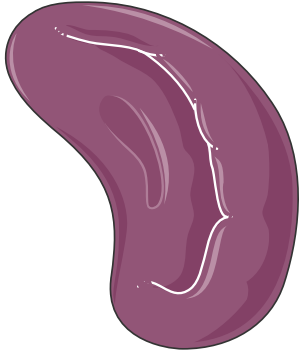
Thrombocytopenia

Favors bleeding

↑ von Willebrand F.
↑ Multimer size

Favors thrombosis

Thrombocytopenia and cirrhosis

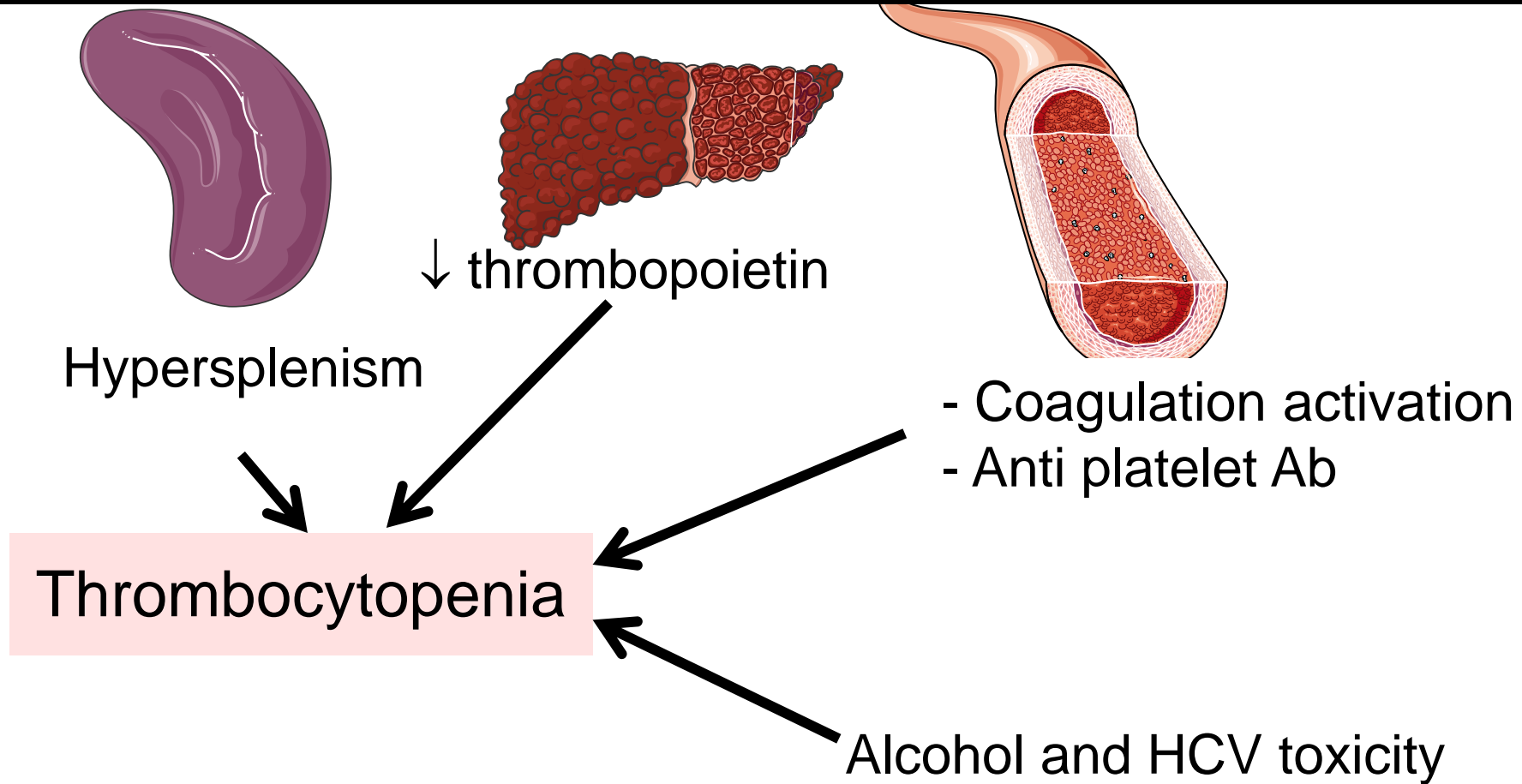


Hypersplenism



Thrombocytopenia

Thrombocytopenia and cirrhosis



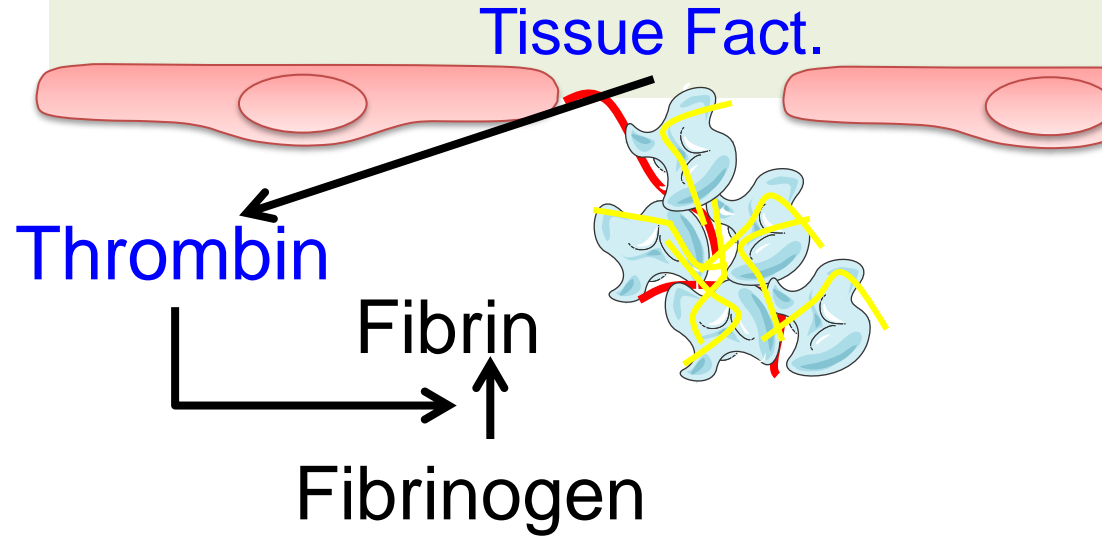
Coagulation in cirrhosis

Primary hemostasis:

platelet aggregation

Coagulation:

fibrin formation



↓ fact II, V, VII, IX,
X and Fg

Favors bleeding

↓ AT, prot C, S,
↓ ↑ factor VIII

Favors thrombosis

Coagulation in cirrhosis

Primary hemostasis:

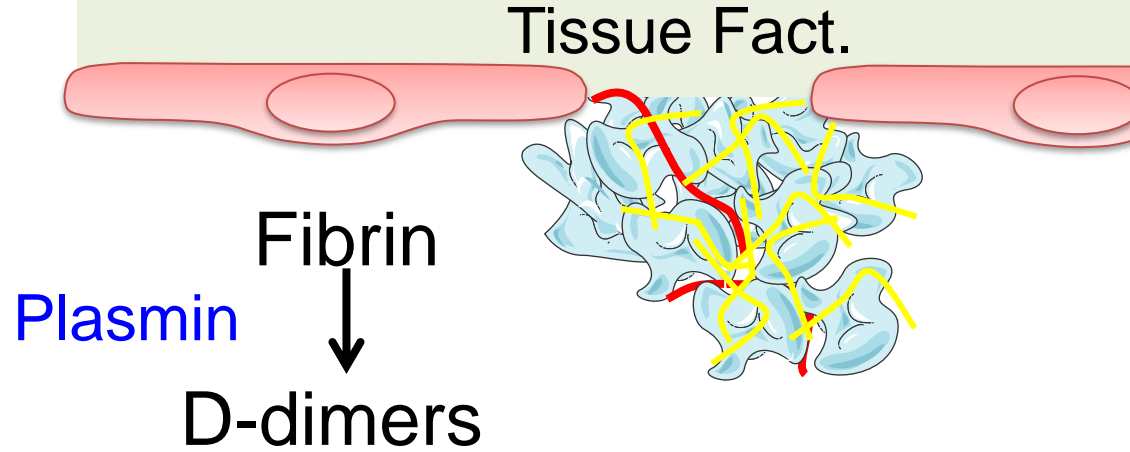
platelet aggregation

Coagulation:

fibrin formation

Fibrinolysis:

fibrin lysis



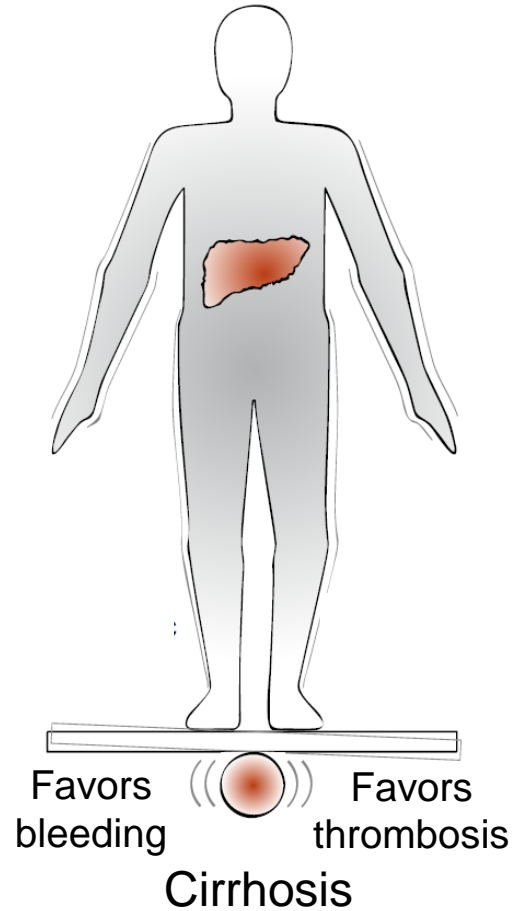
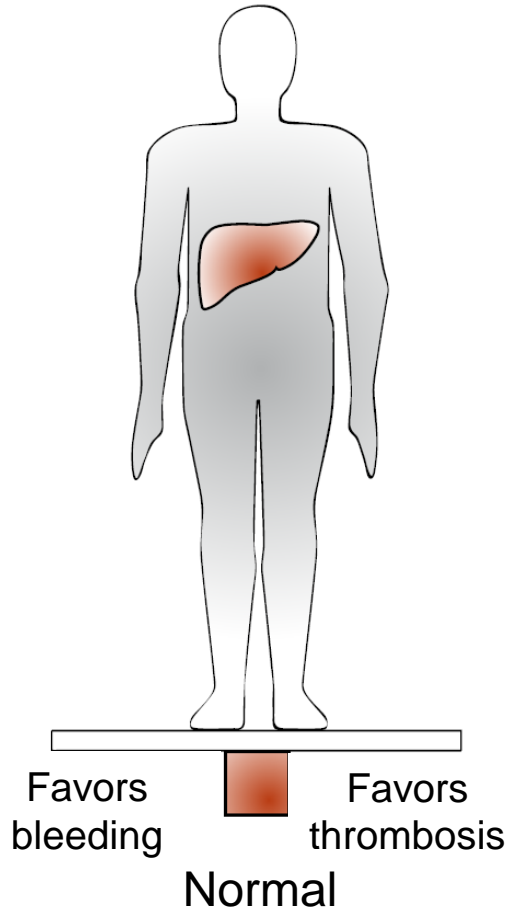
↑ tPA

↓ plasminogen, α_2
antiplasmin, ↑ PAI-1

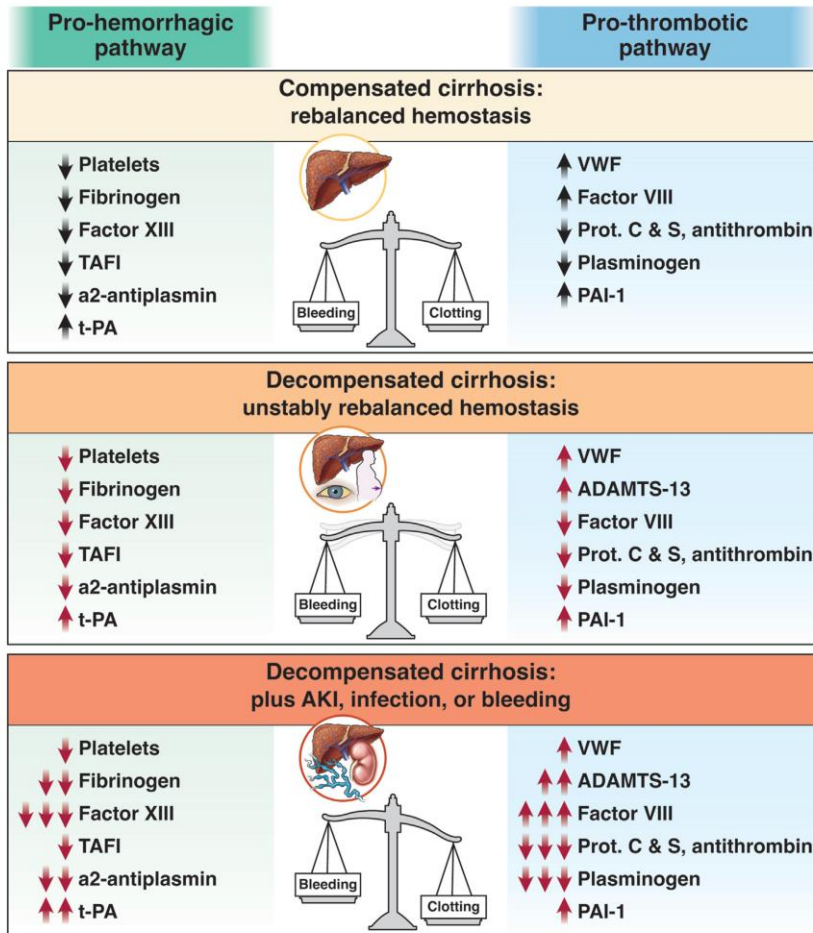
Favors bleeding

Favors thrombosis

Coagulation in cirrhosis



Coagulation changes with cirrhosis progression



Coagulation in cirrhosis



Invasive procedures in patients with cirrhosis

- Coagulation changes in patients with cirrhosis
- Management of invasive procedures in cirrhosis
- Management of anticoagulants and antiplatelet agents

Invasive procedures in patients with cirrhosis

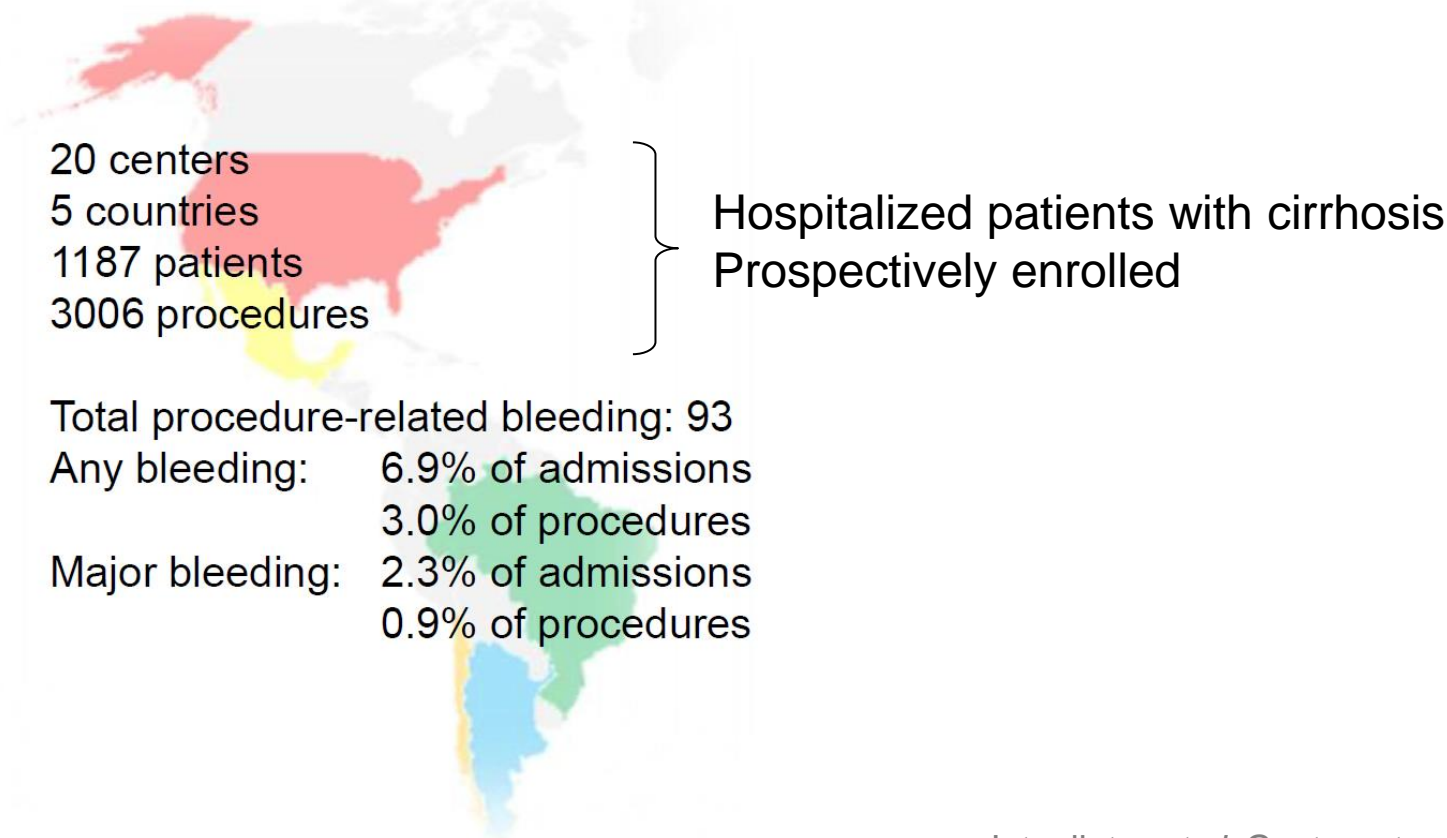
- The patient
- The procedure
- The laboratory

Prediction: the patient

When the procedure is scheduled

- Personal or familial history of bleeding
- Anticoagulants / antiplatelet agents

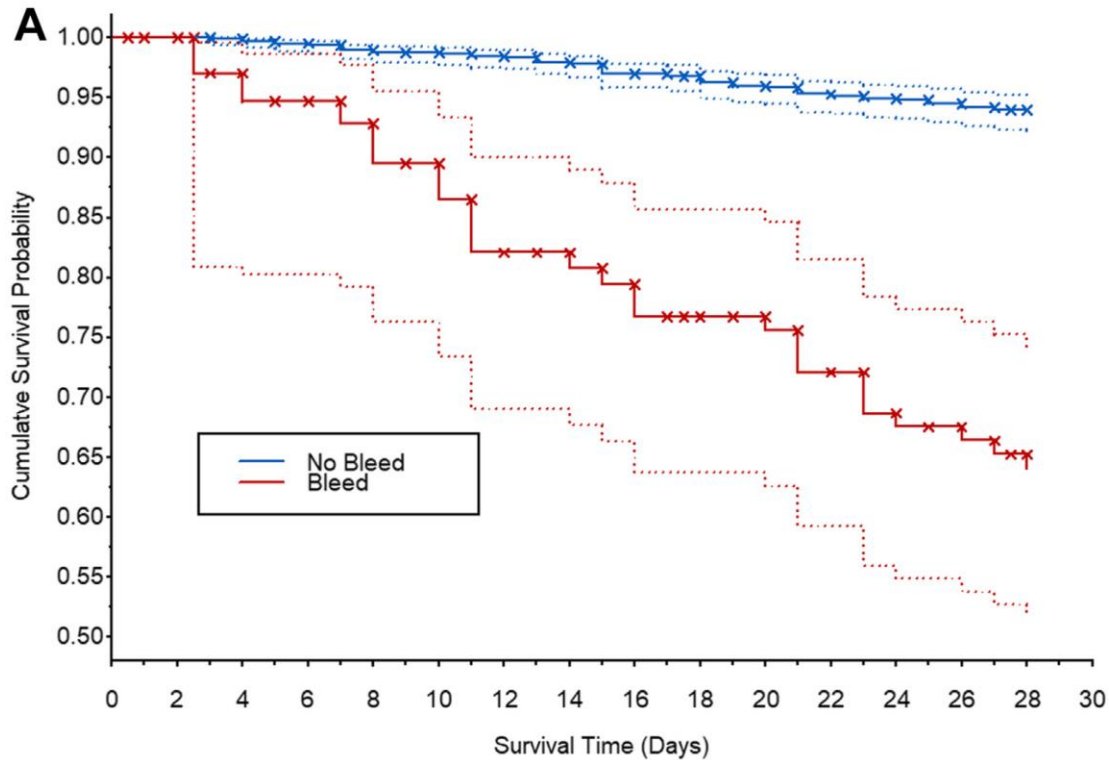
Predictors of bleeding in hospitalized patients with cirrhosis



Predictors of bleeding in hospitalized patients with cirrhosis

| Independent predictors of procedure related bleeding | aOR | P value |
|--|-------------|-----------------|
| Procedure risk | 4.64 | <.001 |
| MELD score at admission | 2.37 | <.001 |
| BMI | 1.40 | .007 |
| Ascites | 1.31 | .062 |
| Trainee | 1.56 | .177 |
| AKI present at admission | 0.72 | .223 |
| INR prior to procedure | 1.22 | .294 |
| Infection at admission | 1.26 | .337 |
| Antithrombotic prior to procedure | 1.34 | .394 |
| Platelet level prior to procedure | 0.93 | .635 |
| Number of prior procedures | 1.02 | .657 |
| ACLF present at admission | 1.04 | .776 |
| VTE prophylaxis at admission | 1.01 | .972 |

Bleeding in hospitalized patients with cirrhosis: a poorer survival



Prediction: the procedure

| Guidelines | Percutaneous liver biopsy | Transjugular liver biopsy |
|-------------------|--------------------------------------|--------------------------------------|
| EASL 2022 | Low | Low |
| ISTH 2021 | High | Low |
| AASLD 2021 | High | High |

Based on same definition: threshold $> 1.5\%$



52 experts

80 invasive procedures



Consensus for 52 procedures

High risk:

- ✓ interventional endoscopy
- ✓ percutaneous biopsies
- ✓ central nervous system

Low risk:

“Can you put the finger?”

Prediction: the laboratory

| | BSG 2020 | ACG 2020 | AASLD 2021 | AGA 2021 | ISTH 2021 | EASL 2022 |
|---|---|---------------------|-----------------------|---------------------|----------------------|----------------------|
| Platelet ≥ 50 × 10⁹/L | Do not correct | | | | | |
| PT/INR | If INR > 1.4, transvenous | Do not correct | | | | |
| aPTT | Not mentioned or do not evaluate | | | | | |
| Fibrinogen | No recommendation / Do not correct / Do not evaluate | | | | | |
| Viscoelastic tests | No specific recommendation / May be useful/ Do not use routinely | | | | | |

➔ Do not correct most coagulation abnormalities

Prediction: the laboratory

| | BSG 2020 | ACG 2020 | AASLD 2021 | AGA 2021 | ISTH 2021 | EASL 2022 |
|---|---------------------|---|-----------------------|---|---|--|
| Platelet < 50× 10⁹/L | Trans-venous | Platelet infusions or TPO rec. agonists | No correction | severe thrombocytopenia and high-risk procedure | very high-risk surgery and <30-50 × 10 ⁹ /L: correct | < 50 × 10 ⁹ /L + local hemostasis not possible: correction possible |

→ Platelet < 50× 10⁹/L should raise attention



52 experts

80 invasive procedures



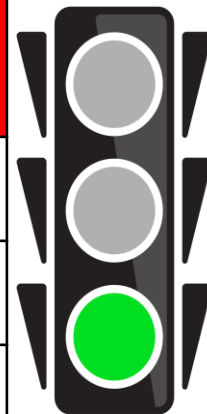
Consensus for 52 procedures

35 at low risk of bleeding

17 at high risk of bleeding

Suggested thresholds

| | Low-risk procedure | High-risk procedure or surgery |
|----------------|----------------------|--------------------------------|
| Platelet count | $> 30 \times 10^9/L$ | $> 50 \times 10^9/L$ |
| INR | Do not measure | $< 2^*$ |
| aPTT | Do not measure | |



A comprehensive work-up for hemostasis changes does not improve prediction of liver biopsy related bleeding

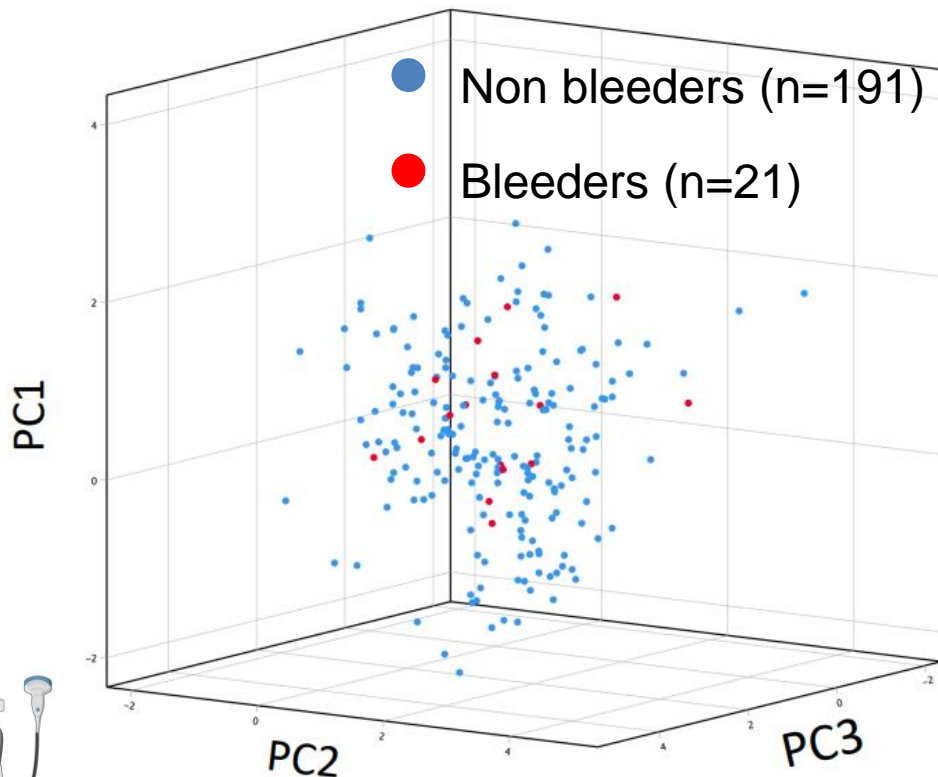
302 patients undergoing liver biopsy



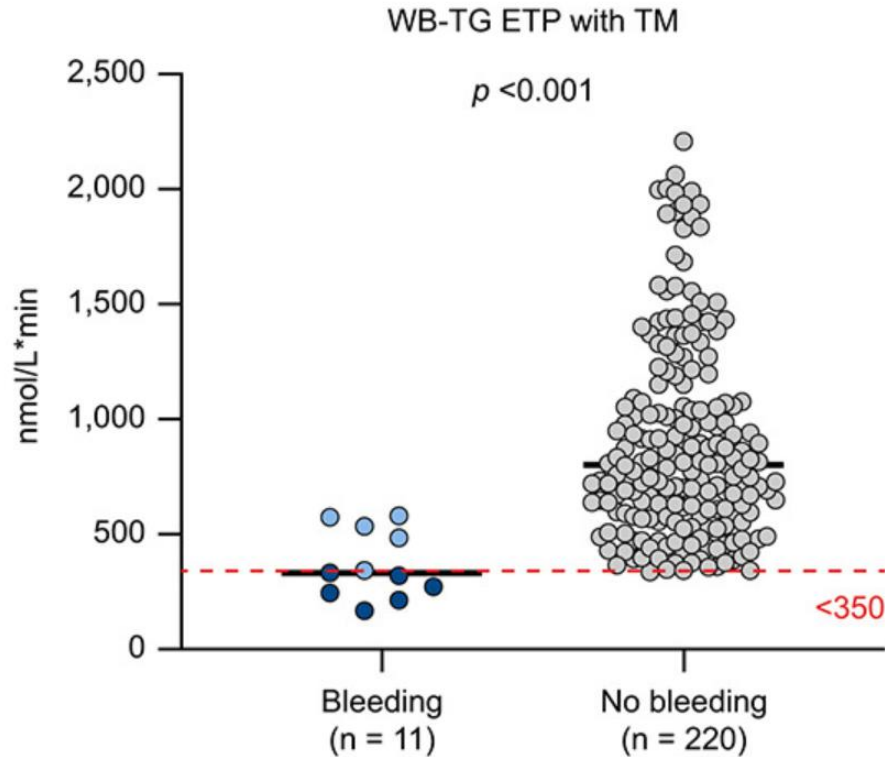
- PT, aPTT, platelet, coag factors
- PFA-100
- Thromboelastography
- Thrombin generation assays
- Plasma clot lysis time
- Clinical questionnaire



Endpoint: liver hematoma or ↓ Hb



Whole blood thrombin generation assay: some potential?



Major Clinically relevant non-major

Going beyond the limits: interest of thromboelastography?

Cirrhosis; INR > 1.8 or PLT < 50'000 /mm³



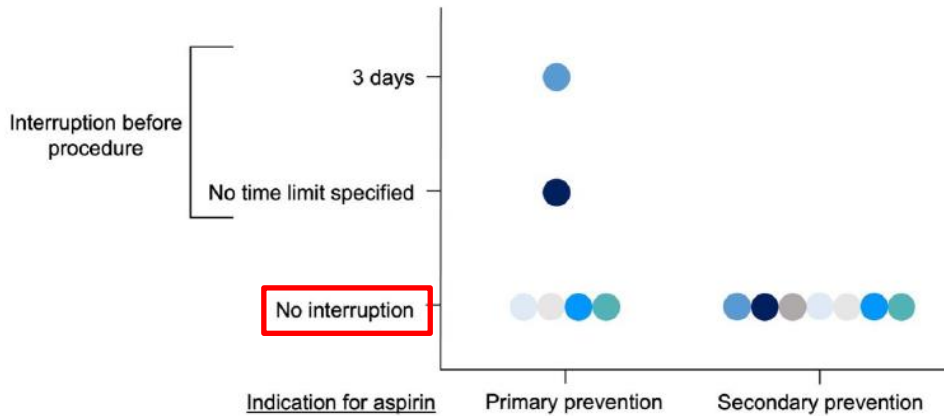
| | SOC (n=30) | TEG guided (n=30) |
|-------------------|------------|-------------------|
| PLT transfusion | 46% | 17% |
| FFP transfusion | 66% | 10% |
| Bleeding | 3% | 0% |
| Allergic reaction | 3% | 0% |

Invasive procedures in patients with cirrhosis

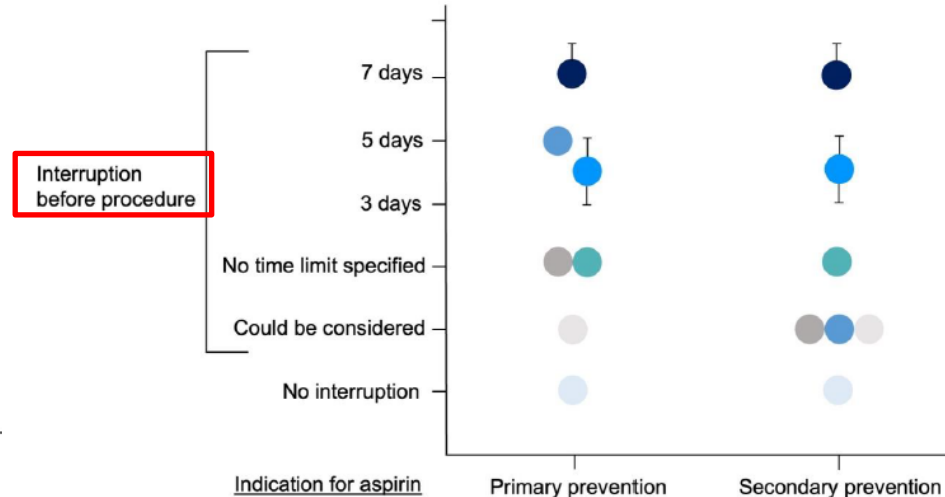
- Coagulation changes in patients with cirrhosis
- Management of invasive procedures in cirrhosis
- Management of anticoagulants and antiplatelet agents

Management of aspirin before invasive procedures

Low-risk procedure



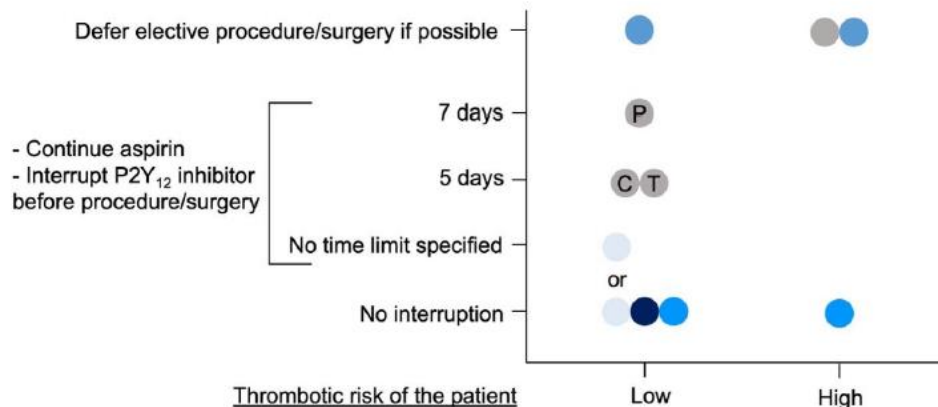
High-risk procedure



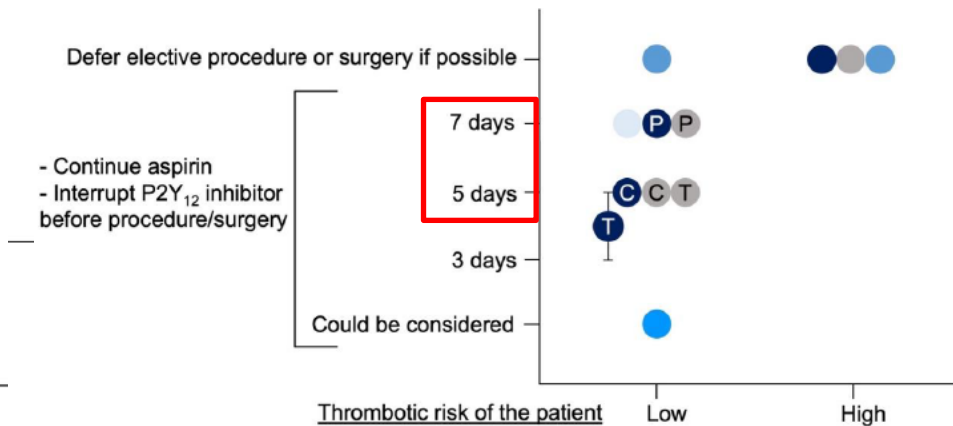
- Halvorsen, 2022³⁰
- Barkun, 2022⁶⁵
- Kietaibi, 2023⁹⁴
- Veitch, 2021⁹²
- Joglar, 2024⁹⁷
- Patel, 2019⁵
- Lester, 2024⁸⁵
- Douketis, 2022⁶³
- Vahanian, 2022⁹⁶

Management of DAPT before invasive procedures

Low-risk procedure



High-risk procedure

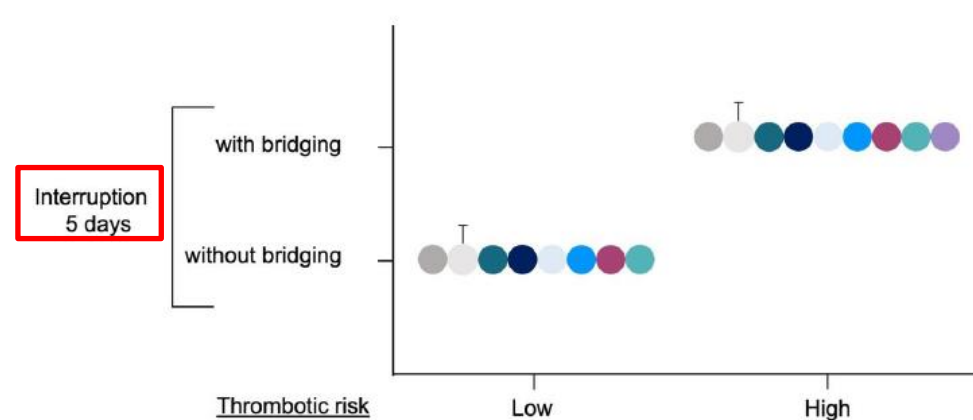
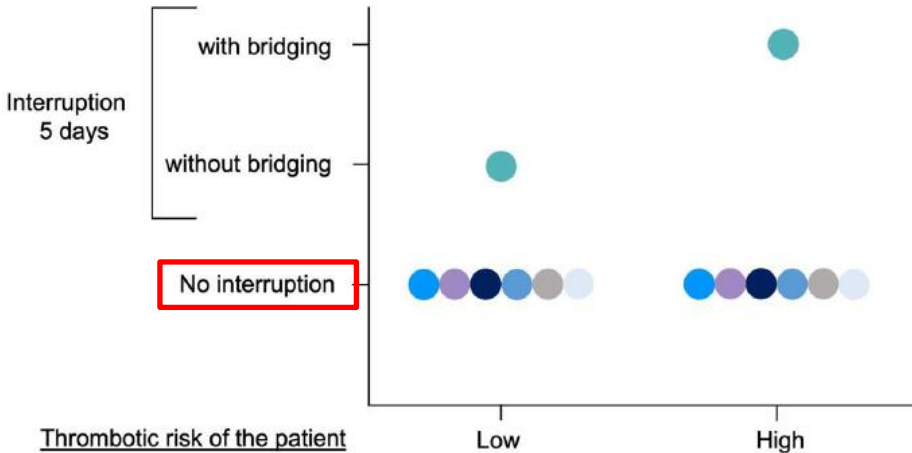


● Halvorsen, 2022³⁹
● Barkun, 2022⁹⁵
● Kietaibl, 2023⁹⁴
● Veitch, 2021⁹²
● Joglar, 2024⁹⁷
● Patel, 2019⁵
● Lester, 2024⁹⁵
● Douketis, 2022⁹³
● Vahanian, 2022⁹⁶

Management of VKA before invasive procedures

Low-risk procedure

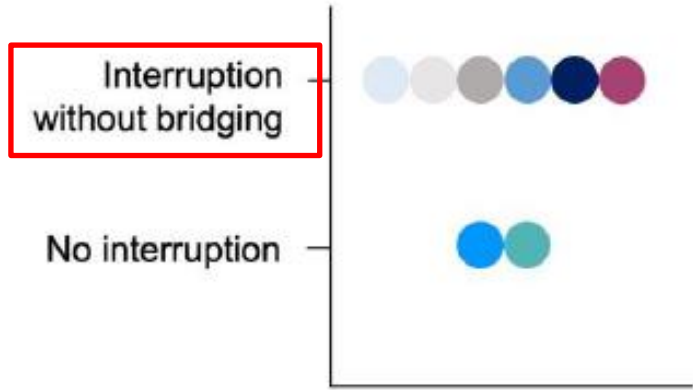
High-risk procedure



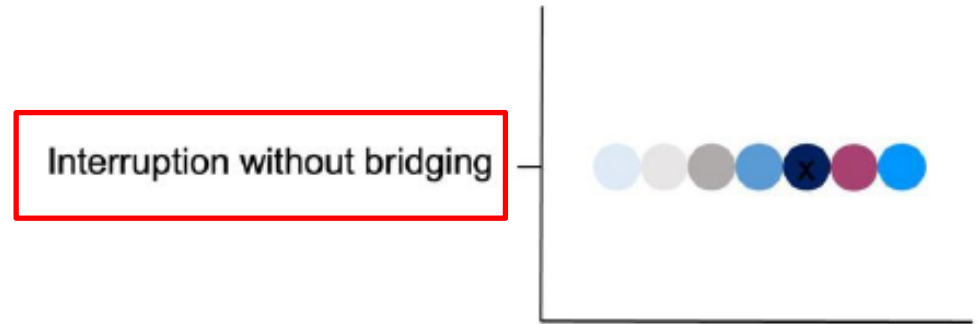
- Halvorsen, 2022³⁰
- Barkun, 2022⁶⁵
- Kietaibl, 2023⁹⁴
- Veitch, 2021⁹²
- Joglar, 2024⁹⁷
- Patel, 2019⁵
- Lester, 2024⁸⁵
- Douketis, 2022⁶³
- Vahanian, 2022⁹⁶

Management of DOACs before procedure
























































Low-risk procedure



High-risk procedure



Management of DOACs and VKA before procedures

| | Day -5 | Day -4 | Day -3 | Day -2 | Day -1 |  | Day +1 | Day +2 | Day +3 | | |
|--------------------|---|--------|---|---|--|---|---|---|---|---|---|
| LOW-BLEEDING RISK | RIVAROXABAN APIXABAN EDOXABAN DABIGATRAN (CrCl ≥50 mL/min) | |  |  |  |  |  |  |  |  |  |
| | DABIGATRAN (CrCl 30-50 mL/min) | |  |  |  |  |  |  |  |  |  |
| | WARFARIN | |  |  |  |  |  |  |  |  |  |
| HIGH-BLEEDING RISK | RIVAROXABAN APIXABAN EDOXABAN DABIGATRAN (CrCl ≥50 mL/min) | |  |  |  |  |  |  |  |  |  |
| | DABIGATRAN (CrCl 30-50 mL/min) | |  |  |  |  |  |  |  |  |  |
| | WARFARIN | |  |  |  |  |  |  |  |  |  |

Treatment of post-procedure bleeding

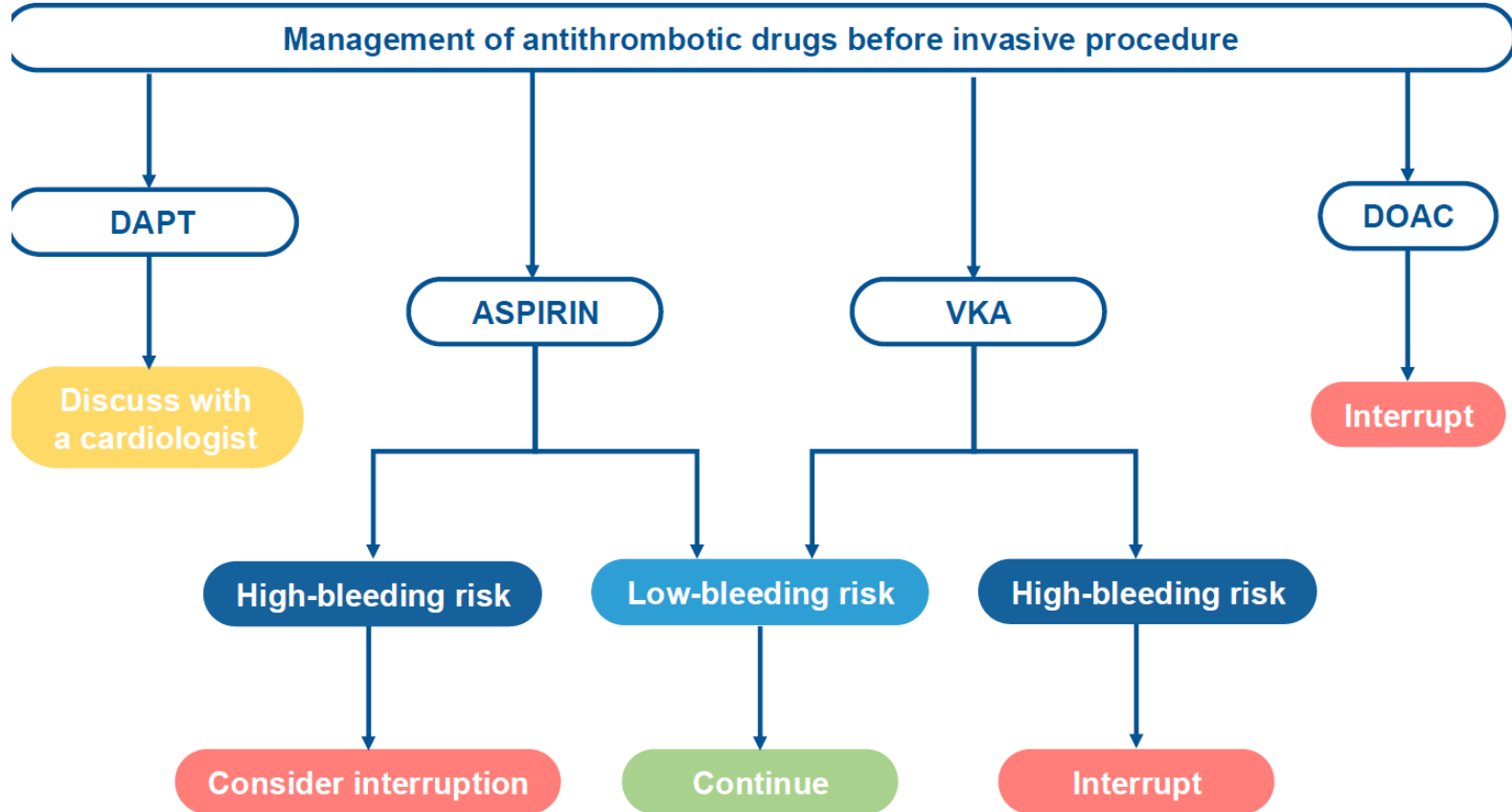
Local treatment +++

| Treatment | Indication |
|---------------------------|--|
| Platelet transfusion | Platelet < 50'000/mm ³ ; Thrombopathy Antiplatelet |
| TPO receptor agonists | Not for acute setting |
| Fibrinogen concentrates | If Fg < 100 or 120 mg/dL |
| Fresh frozen plasma | If hemorrhagic shock |
| Prothrombin complex conc. | If hemorrhagic shock |
| Tranexamic acid | If hyperfibrinolysis |
| Desmopressin | No |
| Recombinant FVIIa | No |

Conclusion #1

- **Cirrhosis:** fragile balance of haemostasis
- **Predict: be careful if**
 - ✓ platelets $< 50'000/\text{mm}^3$
 - ✓ “we can not put the finger”

Conclusion #2



Networks for vascular liver diseases



European Reference Network

Hepatological Diseases (ERN RARE-LIVER)



VALDIG

VASCULAR LIVER DISEASE GROUP



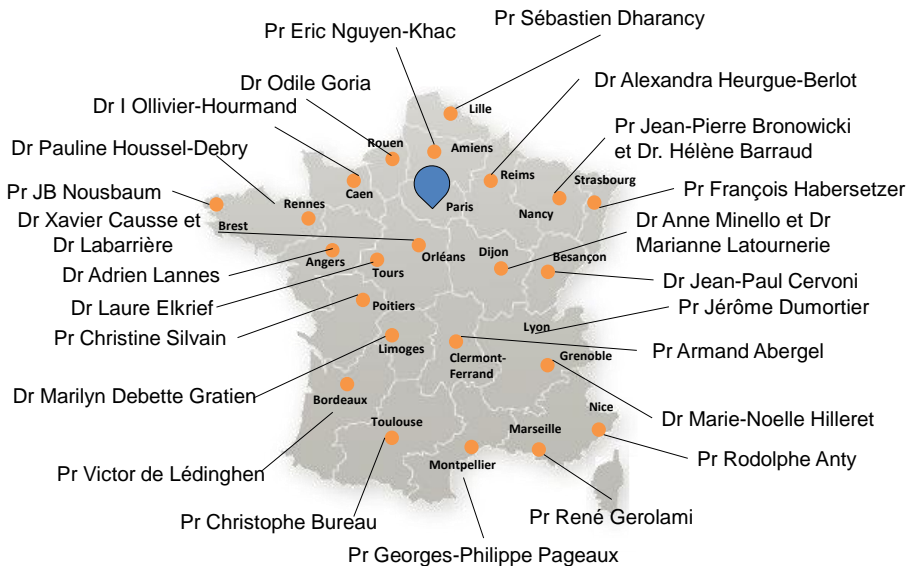
French network for vascular liver diseases



CENTRE DE RÉFÉRENCE MALADIES VASCULAIRES DU FOIE



Centre de compétence maladies vasculaires du foie



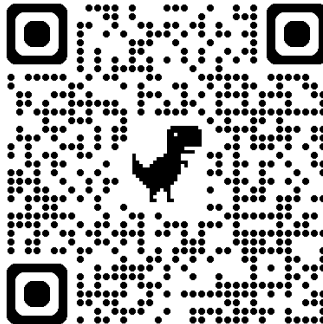
crmvf.foie@bjn.aphp.fr

European vascular liver diseases network

EURO-VALDI-NET

Start Date: 01/11/2024

End Date: 01/11/2028





Instituts
thématiques



Inserm

Institut national
de la santé et de la recherche médicale



Université Paris Cité

CRi
CENTRE de RECHERCHE
sur l'INFLAMMATION



Hepatology unit, Beaujon Hospital
Reference center for vascular liver diseases



Inserm U1149 www.rautoulab.com/
Team "vessels in liver diseases"



Get these slides there:



Les Programmes Hospitaliers
de Recherche Clinique
(PHRC)



