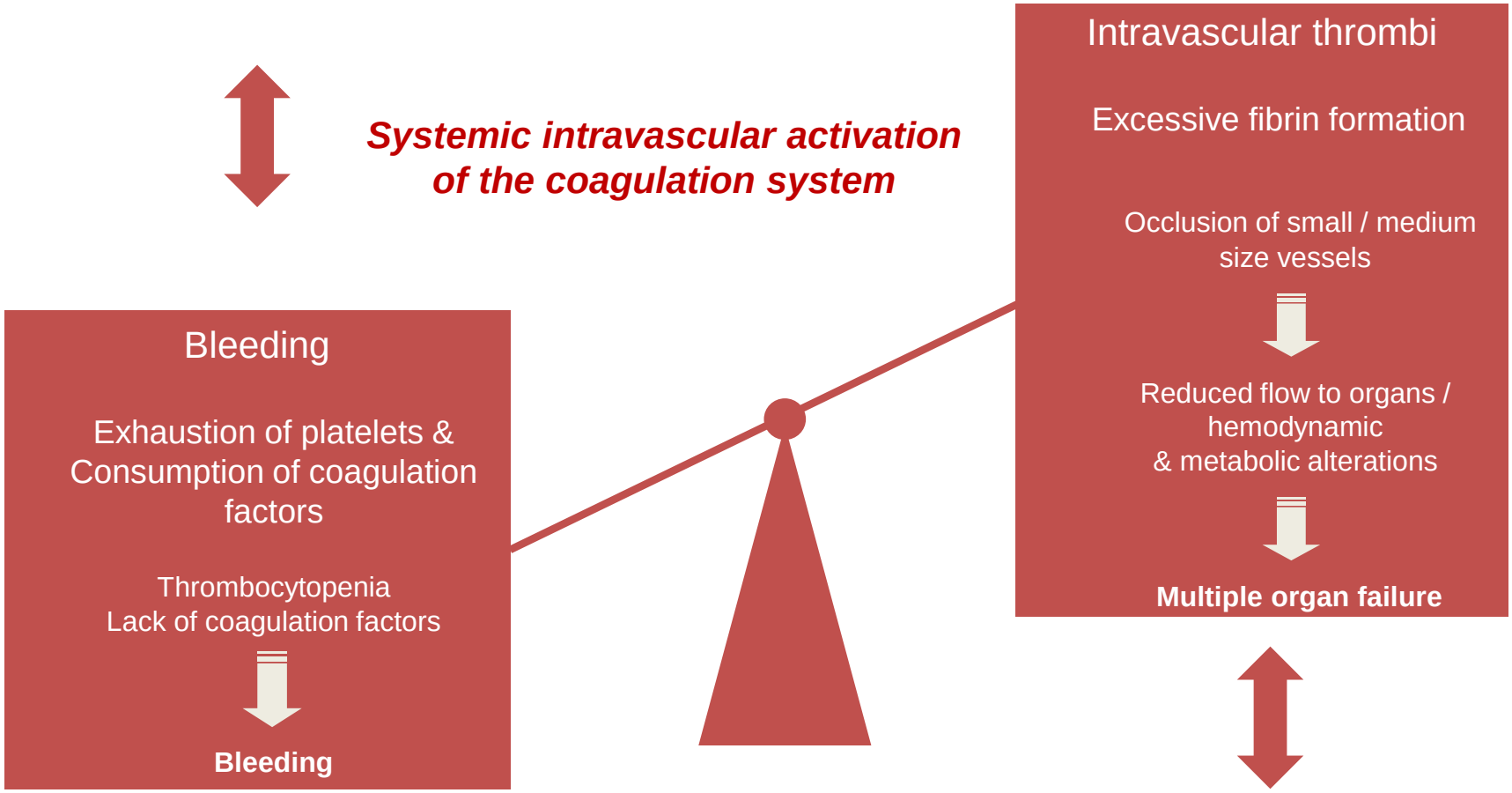
DIC
and Fibrin Related Markers

A comprehensive offer

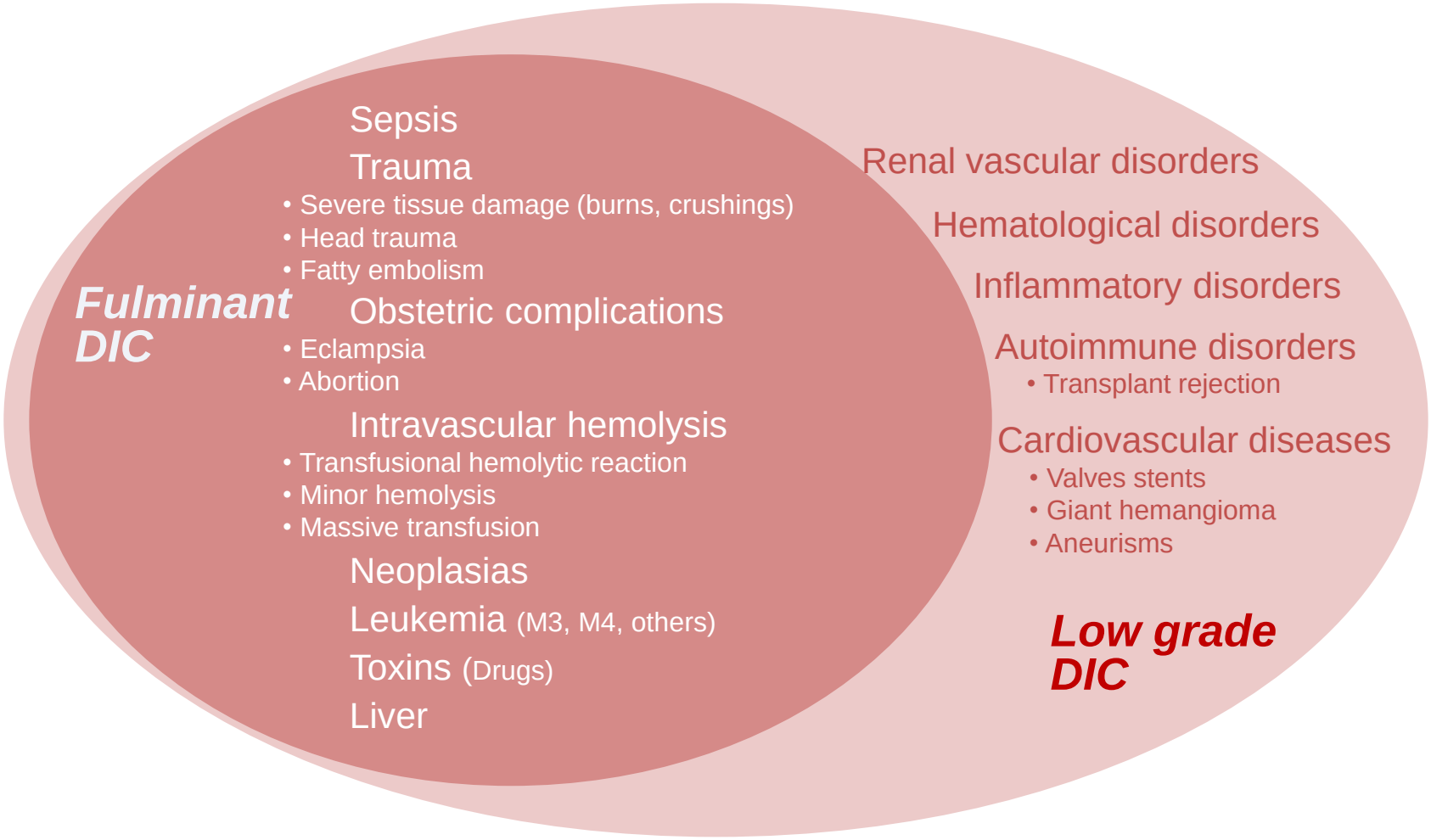
What is DIC?

(Disseminated Intravascular Coagulation)



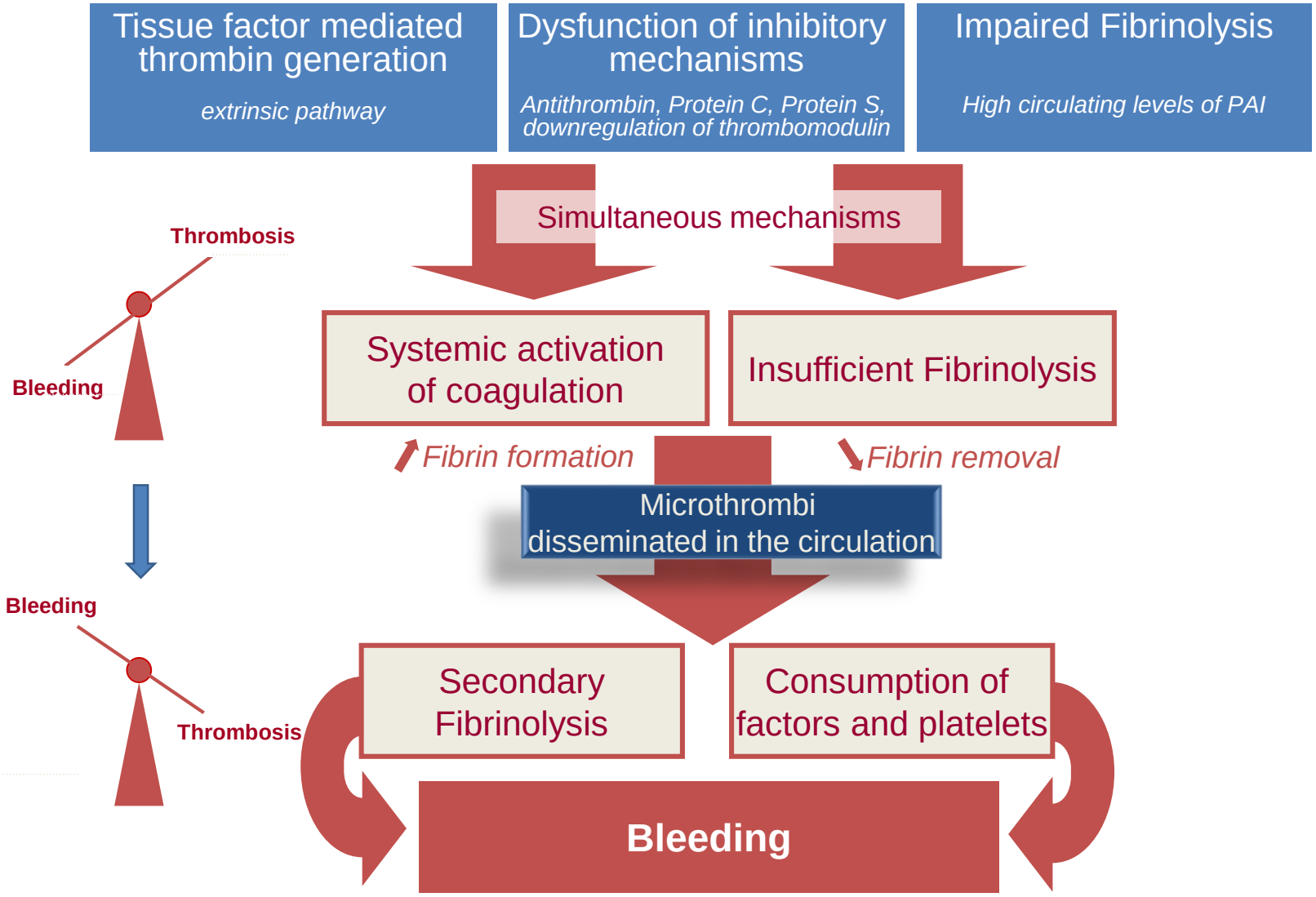
➔ DIC involves a dynamic situation due to an imbalance between procoagulant and anticoagulant proteins

Disorders usually associated with DIC



- ➔ DIC is not a disease itself but is always secondary to an underlying disease
- ➔ DIC is a life-threatening condition

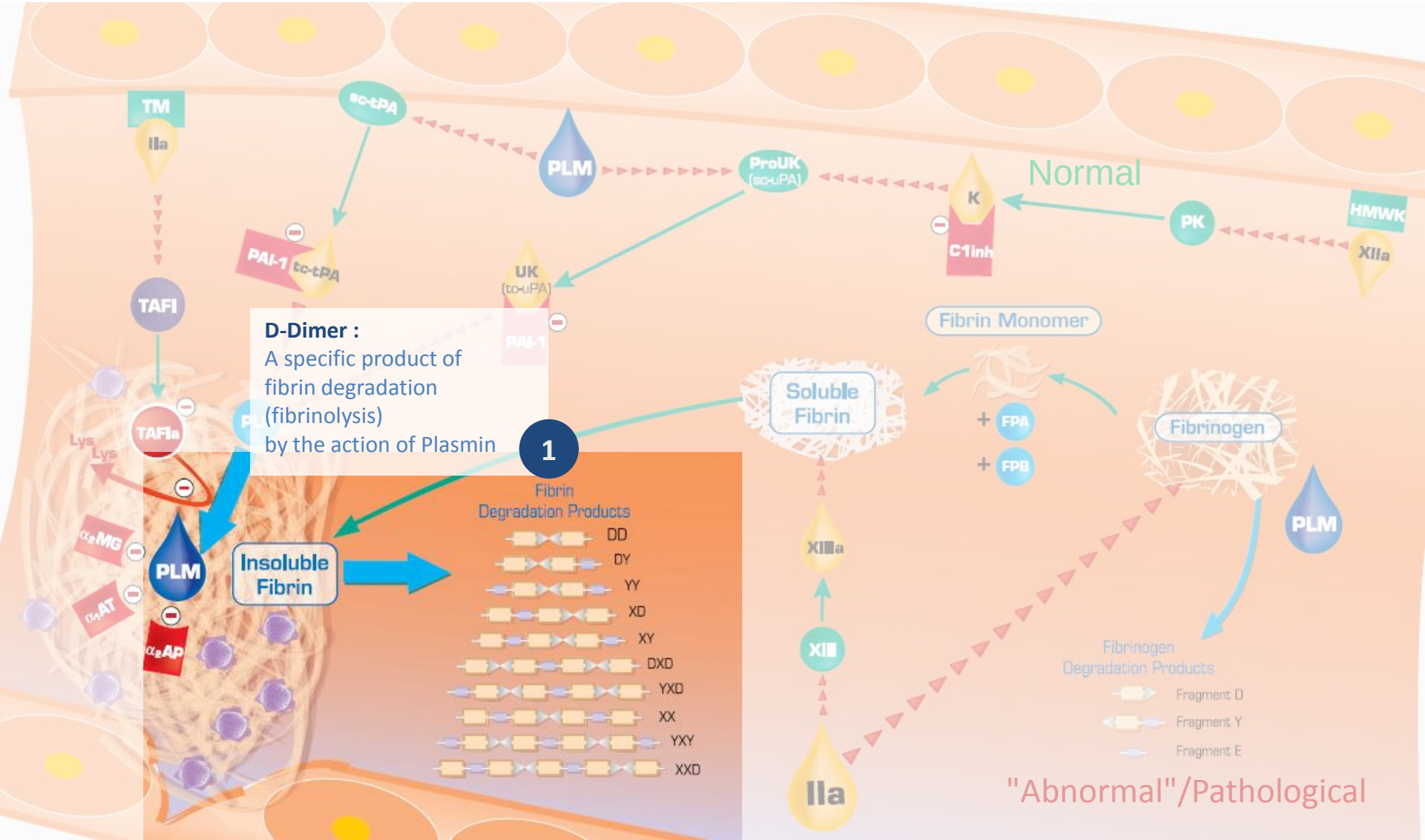
Pathogenesis of DIC



Levi M, De Jonge E, Meijers J. Blood Reviews 2002; 16: 217-23

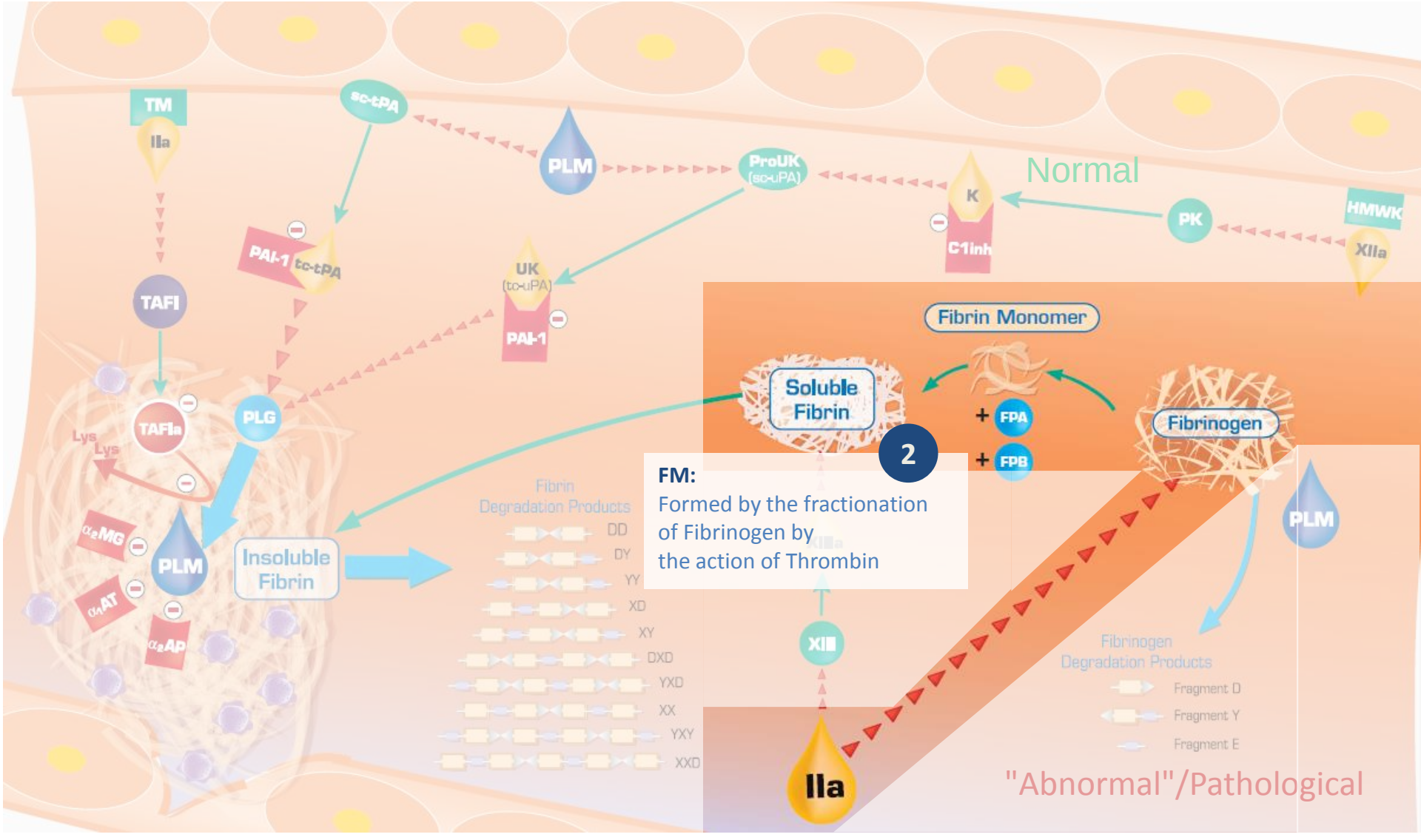
Fibrin-Related Markers

Markers of plasmin & thrombin action (1)



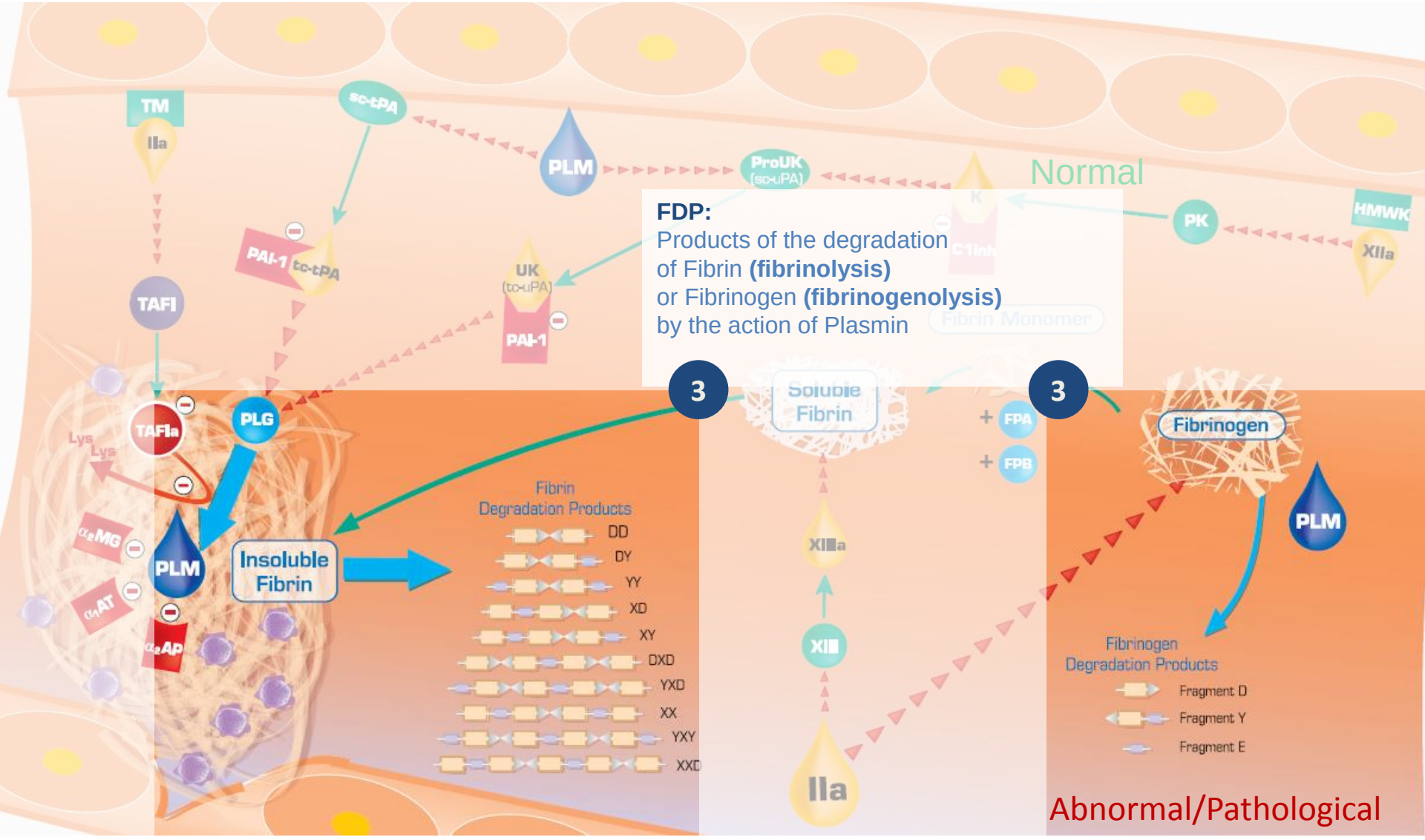
Fibrin-Related Markers

Markers of plasmin & thrombin action (2)



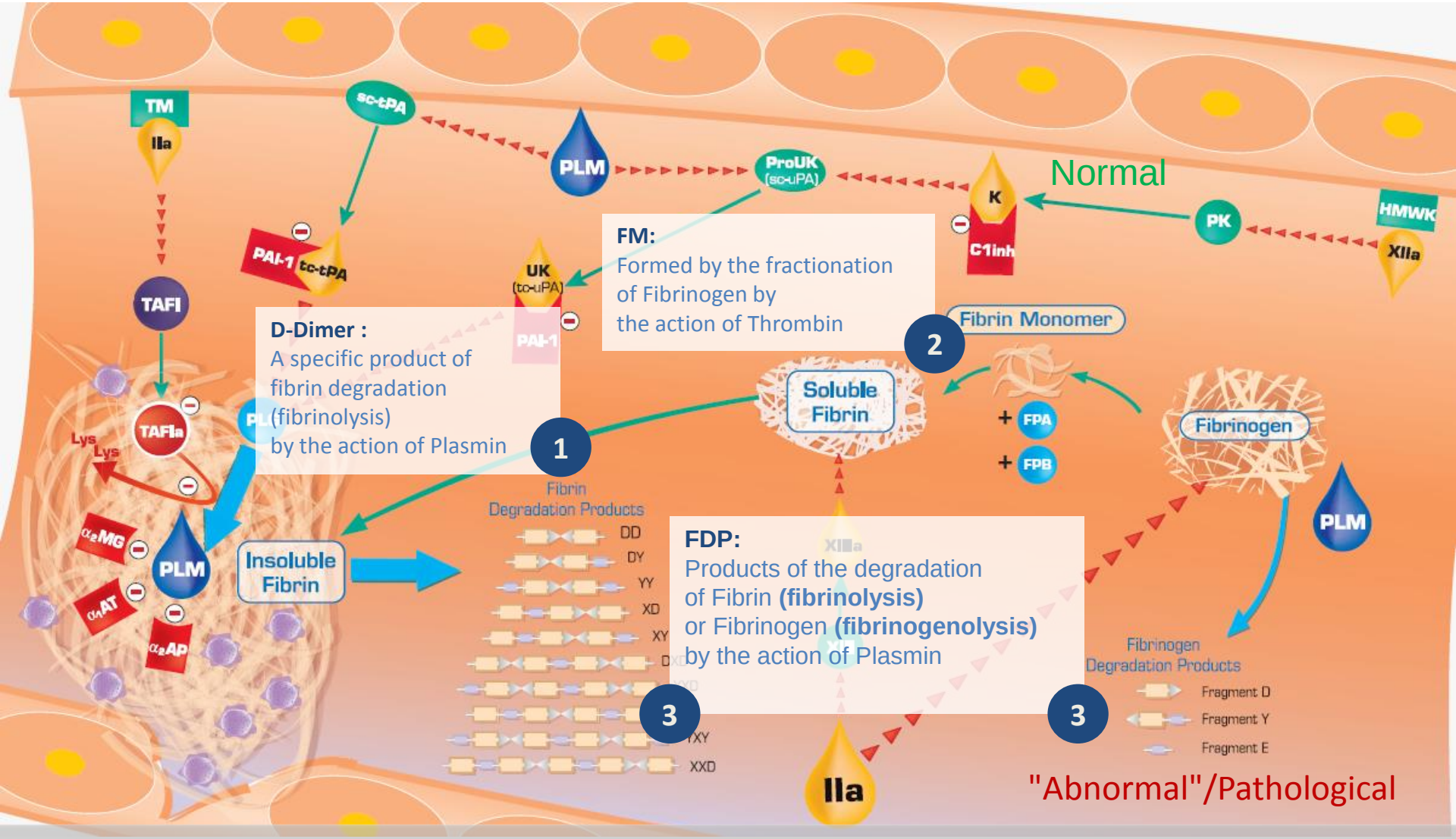
Fibrin-Related Markers

Markers of plasmin & thrombin action (3)



Fibrin-Related Markers

Markers of plasmin & thrombin action



➔ Concomitant generation of Thrombin & Plasmin

➔ Balance between FM and FDP/D-Di

DIC Diagnosis

Key aspects

- Encompass **both clinical and laboratory** information
- The ISTH DIC Scoring system correlates key clinical observations and outcomes
- Repeat tests to monitor the dynamically changing scenario

"Guidelines for the diagnosis and management of disseminated intravascular coagulation", British Society of Haematology, British Journal of Haematology, 2009

Composite scoring systems for DIC

ISTH diagnostic algorithm for overt DIC

1. **Risk assessment: does the patient have an underlying disorder known to be associated with overt DIC?**
   - If yes: **proceed**; if no: **do not use this algorithm**
2. **Order global coagulation tests**
   platelet count, PT, fibrinogen, soluble fibrin monomers or fibrin degradation products
3. **Score global coagulation test results:**
   - platelet count (G/L): >100 = **0** ■ <100 = **1** ■ <50 = **2**
   - prolonged PT: <3 s = **0** ■ >3 s but <6 s = **1** ■ >6 s = **2**
   - fibrinogen level: >1.0 g/L = **0** ■ <1.0 g/L = **1**
   - elevated fibrin-related markers *(e.g. FM, FDP)*:
     no increase = **0** ■ moderate increase = **2** ■ strong increase = **3**
4. **Calculate score**
   - If ≥ 5: **compatible with overt DIC;** repeat scoring daily
   - If < 5: suggestive *(not affirmative)* **for non-overt DIC**; repeat next 1-2 days.

➔ a DIC score encompassing clinical and laboratory evidence showed higher diagnostic performances than any test alone

Taylor FB, Toh CH, Hoots WK, Wada H, Levi M. Thromb Haemost 2001; 86: 1327-30

DIC

Which lab tests are most useful?

Natural Coagulation Inhibitors

Antithrombin (AT), Protein C (PC): Low levels in 90% of DIC patients

Markers of Fibrinolysis

FRMs

Fibrinogen

Coagulation Factors

Global Clotting times

Prolonged PT and APTT: > 95% of DIC patients

Platelet Count

Incidence in DIC patients
< 100G/L:
50 - 60% (critically ill medical patients)
> 80% (surgical and trauma patients)

➔ No single test is sufficiently specific to diagnose or rule-out DIC

DIC score encompass multiple parameters assessment and follow-up

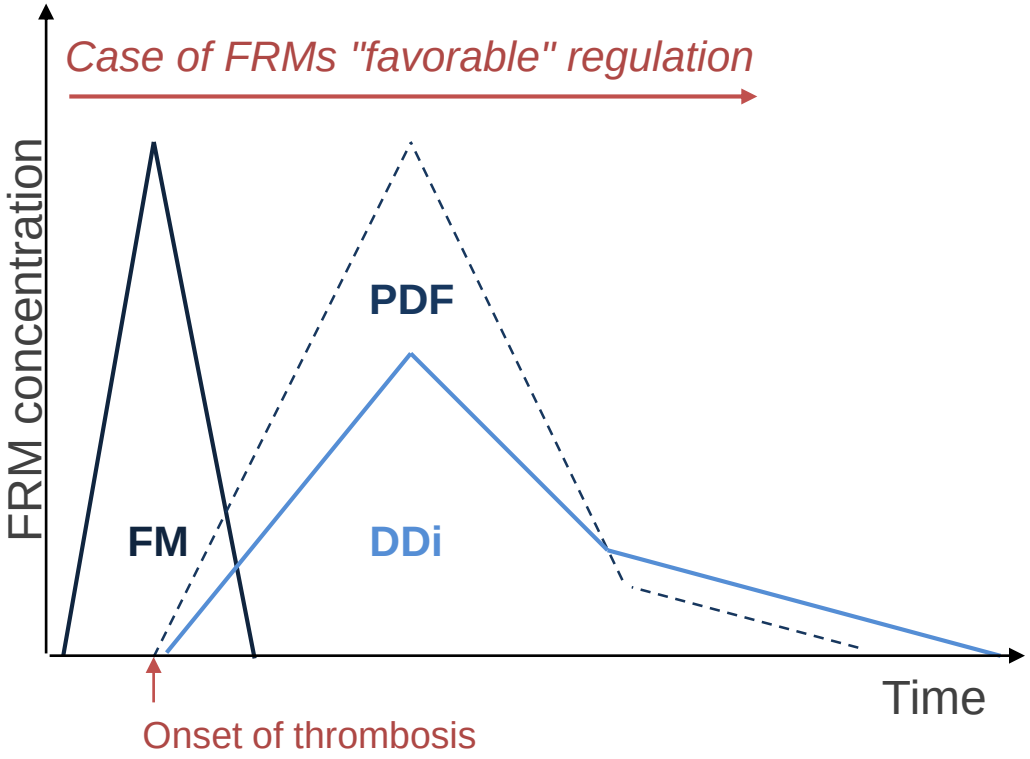
Levi M, Meijers JC DIC: which laboratory tests are most useful. Blood Rev. 2011 Jan;25(1):33-7

DIC
Focus on FRMs

- **Fibrin monomers (FM)**
  - Helpful to diagnose intra-vascular fibrin formation in DIC
  - Above a defined threshold a diagnosis of DIC can be made
  - Only generated intravascularly
    Not influenced by extravascular fibrin formation
    (local inflammation or trauma)
- **Fibrin(ogen) degradation products (FDP)**
  - Detectable in 99% of patients with sepsis and DIC
- **D-dimer (DDi)**
  - High levels in patients with DIC
  - Poorly distinguish patients with DIC from patients with VTE, recent surgery and inflammatory conditions

➔ All FRMs are elevated in hypercoagulable states and may be useful for the diagnosis of DIC

Theorical course of FRMs



In normal conditions, activated thrombin will cleave Fibrinogen into Fibrin Monomers (FM) and fibrinopeptides. FM will form non covalent bindings to form Soluble fibrin polymer.

The plasma FM level will decrease 2 or 3 days after the onset of thrombosis but the D-dimer level will not increase immediately.

All FRMs do not have the same time course

➔ **D-Dimer** and **FDP** reflect secondary fibrinolysis after clot formation

➔ FM reflect the early phase of thrombosis; may be an earlier predictive marker

Adapted from Wada H, Sakuragawa N. Semin Thromb Haemost 2008; 34: 33-8

Study on 105 plasma samples from patients with sepsis, SIRS and healthy individuals*

Toh JMH, Ken-Dror G., Downey C.
Fibrin-Related Marker comparison in Sepsis: Correlation to global and molecular parameters of haemostatic dysfunction.
58th Annual meeting of SSC ISTH, LIVERPOOL, UK , 2012.

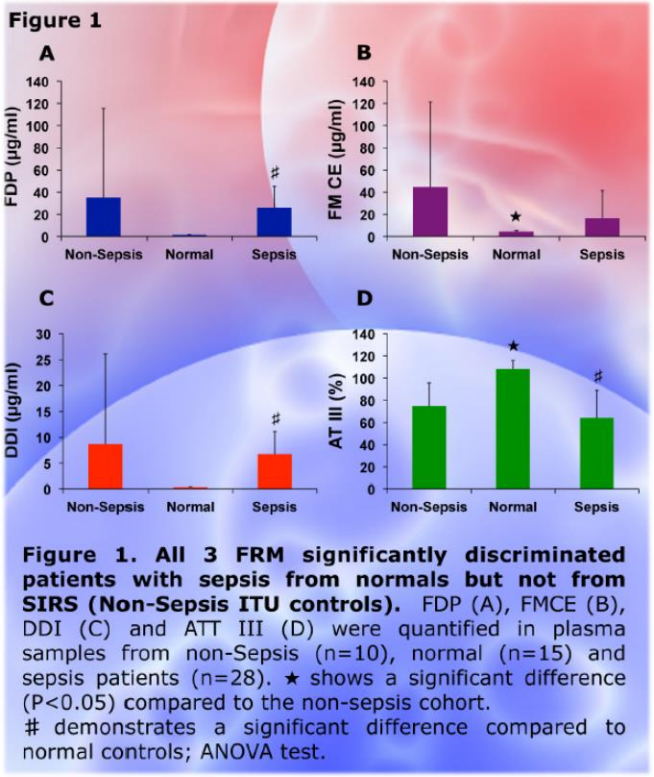


Figure 1. All 3 FRM significantly discriminated patients with sepsis from normals but not from SIRS (Non-Sepsis ITU controls). FDP (A), FMCE (B), DDI (C) and ATT III (D) were quantified in plasma samples from non-Sepsis (n=10), normal (n=15) and sepsis patients (n=28). ★ shows a significant difference (P<0.05) compared to the non-sepsis cohort.
demonstrates a significant difference compared to normal controls; ANOVA test.

➔ Equivalence of the 3 FRM as markers of intravascular fibrinformation with FM performing better in relation to global hemostatic tests *(PT, PLT, FIB)* used in DIC scoring.

*SIRS : Systemic Inflammatory Response Syndrome

FM

Prognosis & Diagnosis value in DIC

1

Wada H, Sakuragawa N,
Are Fibrin –Related Markers Useful for the Diagnosis of Thrombosis?
Seminar in Thrombosis and Hemostasis, 2008; Volume 34; Number 1.

Objectives

Comparison the pathogenesis and course of elevation of FRMs in hypercoagulable states and evaluate their usefulness in the diagnosis of thrombosis.

Outcomes

Timecourse of FRMs after the onset of thrombosis

Findings

Elevated levels of FRMs indicate a high risk of thrombosis providing useful information for the diagnosis; SF may reflect the early phase of thrombosis whereas D-Dimer reflect the secondary fibrinolysis after clot formation.
As they don't have the same dynamic of elevation and decrease relatively to the onset of thrombosis, **both D-dimer and SF measurements may be recommended in patients with DIC**.

2

Gris JC, Faille JL, Cochery-Nouvellon E, Lissalde G, Lefrant JY, J Thromb Haemost, 2011; 9: 1252-5.

Objectives

Prospective study for further asses early FM, DDi and related ISTH overt DIC score values and prognostic values.

Methods

350 patients > 18 years entering ICU with acute septic shock.

Outcomes

Monitoring of survival at 90 days

Findings

A positive overt DIC score using DDi or FM as FRMs were associated with a poor 90-Days outcome; FM being a better prognosis marker.

3

Dempfe CE, Wurst M, Smolinski M, Lorenz S, Osika A, Olenik D, Fiedler F, Borggrefe M.Thromb Haemost, 2004; 91: 812-8.

Objectives
Comparison of the predictive value of the ISTH overt DIC score in a surgical intensive care cohort using either DDi or FM as FRM.

Methods
331 patients - day1 blood sample

Outcomes
Monitoring of 28-day mortality

Findings
FM-DIC score displayed the highest prognostic power.

FM, DDi and FDP:

- ➔ Are elevated in hypercoagulable states
- ➔ Have different time course (FM prethrombotic, FDP/D-Di post-thrombotic)
- ➔ May be useful as part of DIC composite score
- ➔ May be useful prognosis markers in DIC patients

Take home messages

FM, DDi and FDP:

- ➔ Are elevated in hypercoagulable states
- ➔ Have different time courses

  (FM prethrombotic, FDP/DDi post-thrombotic)
- ➔ May be useful as part of DIC composite score
- ➔ May be useful prognosis markers in DIC patients