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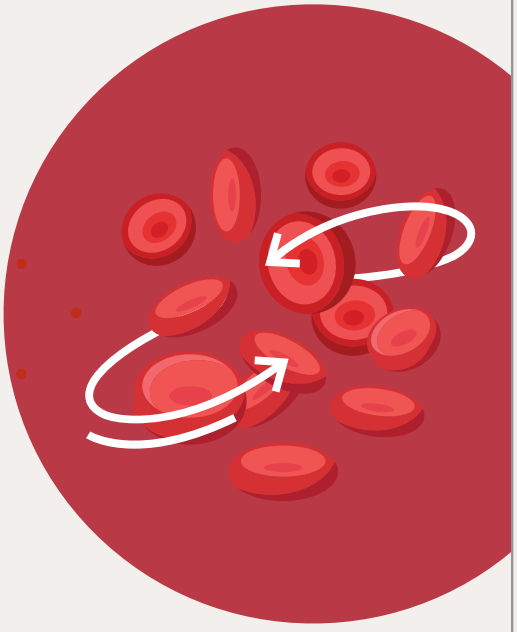

Fibrin-related markers

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PROLOGUE

- The aim of this booklet is to provide key elements on fibrin-related markers (FRM), biomarkers of *in vivo* action of thrombin on fibrinogen and of plasmin on fibrin. This is a rather complicated field due to terminology problems, heterogeneous compounds grouped under the same term, and different epitopes and specificities of monoclonal antibodies used in immunoassays.

- We have used for years good immunoassays (ELISA) and automated immunoturbidimetric assays better suited for clinical use, *i.e.* easy to run 24/7 accessible assays based on monoclonal antibodies with the desired, well-characterized specificity, to measure FRM plasma levels, *i.e.* fibrin monomers (FM) and fibrin(ogen) degradation products, including D-dimer (DDi).

- Laboratory assays for FRM were first used to diagnose disseminated intravascular coagulation (DIC), characterized by the presence of 'soluble complexes' (of fibrin, *i.e.* containing FM) and fibrin(ogen) degradation products (FDP), since there is a subsequent fibrinolytic response, as an attempt to clear the microvasculature of microthrombi contributing to multiple organ failure. Fibrinolysis is exaggerated when there is also a huge release of tissue plasminogen activator (tPA): it can even be so marked that plasmin not only degrades fibrin, but also circulating fibrinogen. By contrast fibrinolysis can be dampened ('shut-down') in case of inflammation and elevated plasminogen activator inhibitor-1 (PAI-1).

- Theoretically, primary hyperfibrinolysis is characterized by elevation of fibrinogen degradation products without that of fibrin degradation products and of FM, *i.e.* there is no evidence of thrombin generation disseminated within the circulation. This is encountered mostly after systemic infusion of plasminogen activators used to dissolve thrombi.

- Cross-linked fibrin degradation products (coined as DDi) have been readily available for years and extensively used for the exclusion of the diagnosis of venous thromboembolic events. The COVID-19 pandemic has revived the interest in FRM to predict the risk of thrombosis, and even of global outcome, in hospitalized patients.

- FRM plasma levels are determined by the relative rates of production and metabolic disposition (distribution in different spaces if applicable, and clearance).

- Small species (FDP with low molecular mass, lower than that of fibrinogen) can cross the intact vascular wall in both directions and can

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be cleared *via* the urinary route. Soluble complexes containing FM are bigger, since they have at least roughly the molecular mass of two fibrinogen molecules. Thus the source of plasma FRM is not necessarily located within the vasculature. It is well known for instance that cross-linked fibrin degradation products recognized through their DDi motif can be elevated in plasma in case of haematomas. In the extravasated blood, thrombin and fibrin are formed, and fibrin is lyzed through tissular fibrinolysis. Small fibrin degradation products can diffuse within the vessels.

- Since all FRM are mixtures of different molecules, distribution and clearance are not easy to determine. Half-lives are rough estimates for those mixtures. The half-life of DDi and FDP within blood is approximately 8 hours, and clearance occurs *via* the kidney and the mononuclear phagocytic system, including the one of the liver. In comparison, the half-life of prothrombin fragments 1+2 is in the order of a few minutes, meaning that bursts of thrombin generation can be easily missed.

- The measurements of related products (=FRM) in the laboratory as biomarkers are of interest in various disorders with coagulation and fibrinolysis alterations.

- There are preanalytical and analytical considerations that should not be overlooked. Preanalytical issues mainly consist in the risk of FRM production during blood sampling and plasma preparation. In the absence of intense circulating fibrinolytic activity however, there should not be artefactual FDP production.

- Immunoassays are based on monoclonal antibodies with specific, well-defined epitopes: for instance neoepitopes in two cross-linked D domains of adjacent FM; or epitopes in the α-chain N-terminal of desA-fibrin, exposed after removal of fibrinopeptide A (FPA) from fibrinogen by thrombin.

- All FRM have in common their heterogeneity, which complicates their measurements. Calibrators cannot perfectly match the heterogeneity, which moreover varies among patients and changes with time in a same patient. Difficulties regarding the units are well illustrated with the specific case of DDi containing FDP. The main result is that assays, even when they share the same units, are not interchangeable.

- As for all immunoassays, interference can be due *e.g.* to elevated bilirubin, haemolysis, or rheumatoid factor and heterophilic antibodies which can lead to spurious results.

- This booklet aims at providing an overview of FRM from an historical, physiological, pathological and clinical standpoints. More detailed information is available from many good reviews and can be obtained from manufacturers.

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INTRODUCTION

Historical perspective (Figure 1)

- In 1666 Marcello Malpighi observed using a single lens microscope that blood clots have a fibrous texture with nerve-like threads. He suggested that these mesh-like structures appear when blood losses its fluidity. These were subsequently named 'fibrin' by Antoine Fourcroy.

- In 1847 the father of coagulation Rudolf Virchow coined the term fibrinogen with the belief that 'ogen' represents a precursor of fibrin.

- In 1872 Alexander Schmidt described the conversion of fibrinogen to fibrin as an enzymatic process.

- In 1879 a great step forward was made by Olof Hammarsten who purified fibrinogen.

- In the 20th century, laboratory assays were set up to investigate 'soluble complexes' containing FM and FDP, but these could not be discriminated. The advent of monoclonal antibodies revolutionized the field of immunoassays, enabling the fine recognition of the various fibrinogen/fibrin related compounds.

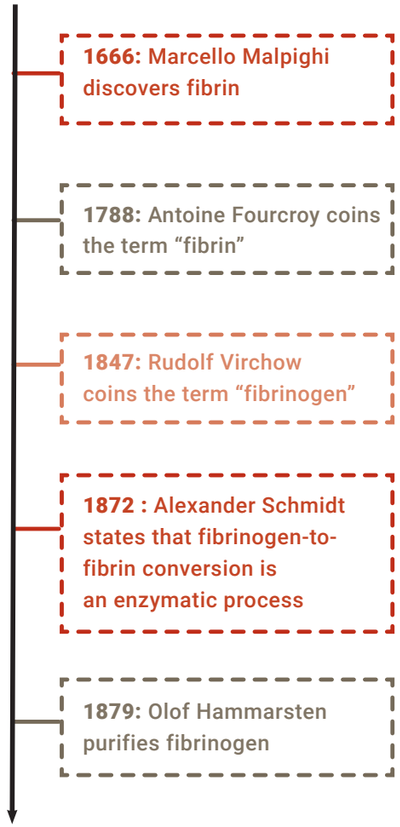

Figure 1. Historical background of FRM *(adapted from De Pieters M, Wolberg A. Res Pract Thromb Haemost 2019; 3: 161-72)*

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Importance of fibrin(ogen)

- The critical role for fibrin in haemostasis is underscored by inherited human afibrinogenemia and dysfibrinogenemias, transgenic fibrinogen knockout mice or mutated mouse models and loss of this protein during trauma.
- Inherited disorders such as haemophilia and factor XIII deficiency, give rise to fibrin clots of insufficient quality due to attenuated thrombin generation or insufficient cross-linking, respectively.
- The essential function of fibrin in haemostasis is echoed by its participation in thrombosis.
- Fibrin is now known to be inextricably linked with several other crucial biological processes including infection and inflammation and wound healing.
- These fundamental biological functions highlight the utility of fibrin and its products as biomarkers.

Fibrinogen

- Fibrinogen is 45 nm long, consisting of two outer D domains each connected by a coiled-coil segment to the central E domain (containing the N-termini of the polypeptide chains).
- Fibrinogen is synthesized in the liver and secreted into the blood, where high concentrations are achieved (2-4 g/L)[1].
- Fibrinogen is a hexamer comprised of two sets of three polypeptide chains: Aα-, Bβ-, γ-chains (A and B refer to fibrinopeptides).

Fibrin formation (Figure 2)

- Fibrinogen is converted to fibrin by thrombin-mediated proteolysis.
- Coagulation is thus thrombin generation followed by fibrin formation.
- N-termini of the Aα-chains of fibrinogen house a FPA sequence, which is cleaved by thrombin to initiate fibrin assembly through exposure of a polymerization site.
- Fibres align in a staggered overlapping arrangement forming double stranded twisting fibrils.
- Cleavage of the N-termini of the Bβ-chains, termed fibrinopeptide B (FPB), occurs more slowly and promotes lateral association.
- Fibrin polymerization proceeds *via* half-staggered interactions that lead to two-stranded protofibrils aggregating laterally to make fibres, which branch to form a three-dimensional network[2].

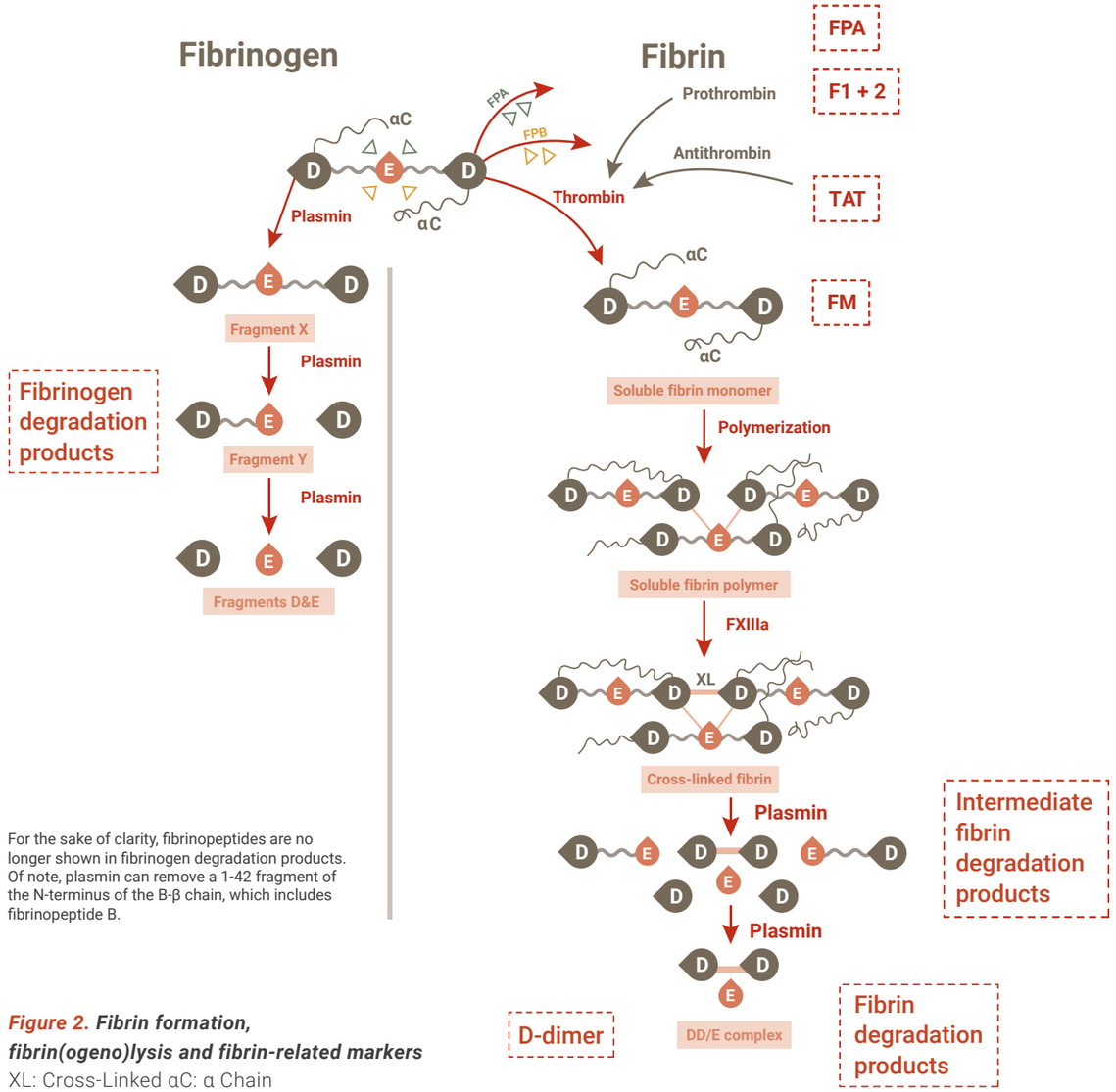

Figure 2. Fibrin formation, fibrin(ogeno)lysis and fibrin-related markers
XL: Cross-Linked αC: α Chain

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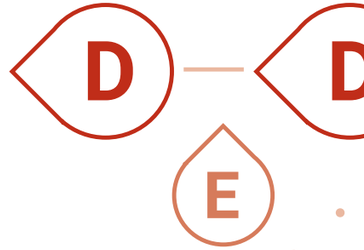
- The tranglutaminase enzyme, factor XIII, is activated by thrombin and introduces ε(-γ-glutamyl)-lysyl covalent bonds between fibrin strands to protect the clot against mechanical stress[3,4].
- Simultaneously inhibitors of fibrinolysis, particularly α_2-antiplasmin, are also cross-linked into the forming fibrin mesh to protect against premature proteolytic degradation[5,6].

Fibrin degradation (Figure 2)

- Fibrin is degraded by the serine protease plasmin that cleaves after lysyl or arginyl bonds.
- Plasmin is formed from circulating zymogen plasminogen by the action of plasminogen activators, tPA and urokinase plasminogen activator (uPA).
- Fibrin acts as a cofactor in its own dissolution, as it binds tPA and plasminogen accelerating plasmin formation by around 1,250-fold.
- The degradation pattern of fibrin is essential to our understanding of what is measured in assays of fibrin-related markers[7]. Cleavage sites have been revealed by study of purified fibrinogen, as it is soluble and easier to analyse.
- Plasmin degradation of fibrin occurs with the same cleavage pattern as fibrinogen, indicating that no major structural reorganisation occurs during fibrin polymerisation[8].
- Following cross-linking by factor XIIIa different degradation products arise.
- The DDi motif consists of two D domains from adjacent FM, cross-linked *via* their γ-chains remnants. This covalent dimer bound non-covalently to fragment E is the DD/E complex. This fragment also occurs in arrays held together by uncleaved coiled-coils[9].
- Larger fibrin degradation products can reassociate with one other and with fibrin[10]; their clearance occurs *via* the kidney and also the liver, depending on the actual fragment[11,12].
- In rare pathophysiological circumstances or when a plasminogen activator is infused as an attempt to lyse thrombi, excess plasmin generation gives rise to systemic fibrinogenolysis (*i.e.* fibrinogen degradation).
- Conversely in some settings such as sepsis, fibrinolysis can be shut down, *e.g.* due to elevated plasma levels of the main inhibitor of plasminogen activators, which is PAI-1.

Clinical utility of fibrin-related markers

- Given the fundamental role of thrombin and fibrin in haemostasis, measurement of plasma levels of FRM (defined in the introduction of the booklet) in diverse settings is highly informative.
- FRM can be measured with immunoassays.
- FRM have different characteristics that govern their informative value in different settings (see specific chapters about clinical value).
- Circulating FPA and FM levels depend only on the coagulation side of the process, equating to evidence of thrombin generation *in vivo*.
- Other biomarkers of thrombin generation *in vivo* are FPA, prothrombin fragments F1+2 (thrombin generation *per se,* since the fragment is the cleavage product of prothrombin when converted to thrombin) and thrombin–antithrombin complexes (TAT) (antithrombin being the main natural inhibitor of thrombin).
- FDP, including those with the cross-linked DDi motif, rely on the activity of plasmin. They bestow insight into fibrinolysis beyond thrombin generation, illustrating the dynamic process of fibrin formation and degradation in some settings.
- In some settings a ratio of thrombin activity (*i.e.* FM or FPA) *vs* FDP (broad sense) or DDi containing FDP might be helpful to give an overall perspective of fibrin turnover in the body.



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D-DIMER

- Fibrin DDi is the final product of fibrinolytic degradation of cross-linked fibrin. Its half-life is approximately of 4-6 hours[13] and its plasma levels are the balance between production and catabolism. Elevated DDi levels are present in all the conditions, physiological (such as elderly or pregnancy) or pathological, in which fibrin production is increased or renal elimination is impaired.

- DDi results are interpreted as negative/positive instead of normal/abnormal.

- Usually, the reports of clinical laboratories give a reference value for DDi assay of <500 ng/mL (or <0.50 µg/mL), which historically is the plasma DDi level adopted in most clinical studies to exclude venous thromboembolism. However, it is necessary to consider that DDi assays are mostly performed in clinical practice to assess the probability that a suspected clinical condition is absent or present. For this reason, the results of DDi assays are more often defined as negative, when the detected levels are below a prespecified threshold value and do not give evidence of the presence of the suspected condition, or positive, when the results are above the prespecified threshold value and therefore are compatible with the presence of the condition. The threshold levels used to separate negative from positive DDi results are proposed by the various clinical studies and are different according to the results of the studies and to the investigated clinical conditions.

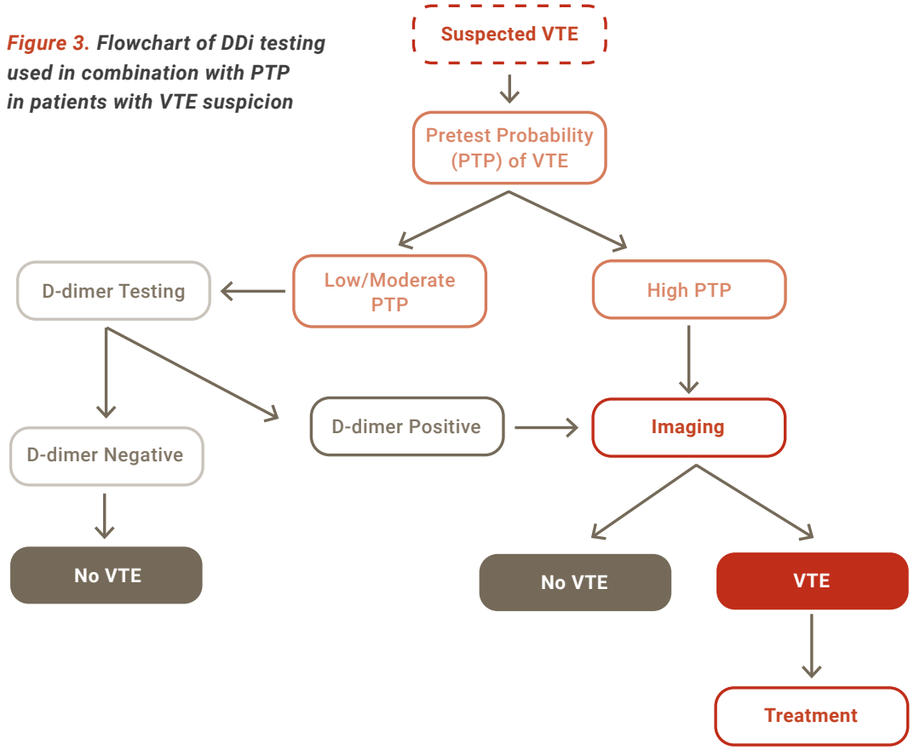
Current validated indications

Exclusion of venous thromboembolism (VTE)

- DDi has proven to be an effective tool for VTE exclusion in selected patients when the DDi level is below a certain validated threshold (then considered as negative DDi) because of its high negative predictive value. On the opposite a DDi level above this defined threshold (so said positive DDi) is not informative of the presence of a thrombus because of the low positive predictive value of high DDi levels in this setting. This latter situation may occur when there are fibrin deposits in the absence of thrombosis.

- The sensitivity of DDi assay for VTE is very high but specificity is rather low. The test is used in suspected patients to help rule-out an acute VTE if results are negative. The advantage of exclusion is to avoid as far as possible the need for costly and sometimes invasive diagnostic imaging tools. To this end, DDi testing should not be used alone and should be performed only when the pre-test clinical probability (PTP) is unlikely or low/moderate. The test should not be used when the PTP is likely or high.
The rationale for non-using DDi testing in these conditions is two-fold: first, the prevalence of the disease (deep vein thrombosis -DVT- or pulmonary embolism -PE-) is very high (≥50%[14]) when PTP is likely or high; and second, because false negative results cannot be excluded in this patient population (Figure 3).

Figure 3.** **Flowchart of DDi testing used in combination with PTP in patients with VTE suspicion



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- Many commercial assays are available. However, the US Food and Drug Administration (FDA) has established that, to be used for this purpose, an assay should have a sensitivity ≥95% (lower limit 95% CI ≥90%) and a negative predictive value (NPV) ≥97% (lower limit 95% CI ≥95%). The FDA has also called for specifically designed clinical management studies for VTE exclusion to establish approval/clearance criteria for "exclusion". Results of DDi assays may be expressed as fibrinogen equivalent units (FEU, the cut-off level is generally 500 ng/mL, or 0.50 µg/mL), or as DDi units (cut-off value about 250 ng/mL, or 0.25 µg/mL).

- DDi assays can give false negative results (Box 1). Conversely, DDi levels increase in all conditions associated with increased fibrin formation (see Table 2 in FDP section) with non-specific positive results. This limitation is particularly important in case of elderly subjects, a population with high prevalence of suspected VTE. Different diagnostic approaches have been validated in case of suspected PE to increase the usefulness of DDi testing in this population.

- The **"age-adjusted"** strategy: DDi cut-off value is calculated in relation to age. In patients aged 50 years or more, the age-adjusted cut-off values are calculated by multiplying the age x 10, when the assay results are expressed as ng/mL, or dividing the age by 100 in the case results are expressed as µg/mL. In this way, a 70-year-old patient would have a cut-off level of 700 ng/mL (or 0.70 µg/mL), instead of 500 ng/mL (or 0.50 µg/mL)[15].

- The **"clinical probability-adjusted cut-off"** strategy. This strategy has recently been proposed by Kearon *et al*. for the diagnostic process of PE[16]. Different threshold of DDi levels in relation to the PTP evaluation (YEARS) are proposed: in patients with a low PTP the cut-off value used to identify negative results (to exclude the disease) is twice the regular cut-off value (<1,000 ng/mL instead of <500 ng mL), whereas in patients with a moderate PTP evaluation, the cut-off used to identify negative results is the usual one (*e.g.*, 500 ng/mL). In this way, the need for chest-imaging studies can be reduced in patients with low PTP, without an increase in undiagnosed PE.

Disseminated Intravascular Coagulation (DIC) diagnosis (Box 2)

- DIC is characterized by a diffuse activation of coagulation, leading to intravascular fibrin formation and deposition, with obstruction of microvasculature, that may result in organ dysfunction (skin necrosis, renal insufficiency, acute respiratory distress syndrome, and circulatory failure). Bleeding may occur, mainly due to consumption of clotting factors.

- Though no diagnostic algorithm is universally accepted, that proposed by the International Society on Thrombosis and Haemostasis (ISTH) is the most frequently used, in which DDi results represent a key factor.

Box 1

Possible causes of false negative D-dimer results

- Insufficient method sensitivity
- Wrong cut-off value
- Concomitant anticoagulant treatment
- More than 7 days from initial signs/symptoms
- Distal DVT
- Isolated subsegmental PE

Box 2

ISTH algorithm for DIC diagnosis

(modified from Toh *et al.*[17])

The ISTH recommended algorithm for DIC diagnosis should be used only if the patient has an underlying disorder known to be associated with overt DIC.

Score based on test results

- Platelet count:
  >100 G/L= **0** <100 G/L = **1** <50 G/L = **2**
- DDi*:
  no increase = **0** moderate increase = **1**
  strong increase = **2**
- Prolonged prothrombin time:
  <3 sec. = **0** >3 to 6 sec. = **1** >6 sec. = **2**
- Fibrinogen:
  >1.0 g/L = **0** <1.0 g/L = **1**

Interpretation of calculated score

If ≥5: compatible with overt DIC (to be repeated daily)
If <5: suggestive for non-overt DIC (to be repeated in 1-2 days)

* Proposed cut-off values: moderate increase: >3,000 ng/mL; strong increase: 7,000 ng/mL. For reagent-specific cut-off values, please refer to: Suzuki K *et al.* J Thromb Haemost 2018; 16: 1442-4.

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Possible future indications

D-dimer and COVID-19 pandemic* (Box 3)

- The disease is characterized by a marked derangement of hemostasis, leading to hypercoagulability, with associated signs of hyperinflammation. The disease has been identified as thrombo-inflammation, resulting in frequent occurrence of macro-thrombosis (especially venous) and of micro-thrombosis (more frequently in pulmonary microvascular bed) with fibrin deposits in the pulmonary alveoli.
- Increased DDi is the most common coagulation abnormality, present even on admission in one-third of patients. The alteration is associated with severity of infection.
- However, lack of standardization (especially for very high DDi levels) across the commercial assays have frequently been reported within the published studies, which makes the comparison of study results at times difficult[18,19].

Prediction of venous thromboembolism recurrence risk (Box 4)

- VTE events tend to recur after anticoagulation treatment is stopped (Figure 4). The risk is higher when the event is unprovoked or associated with weak risk factors, and in male patients. Guidelines recommend these patients be considered for long-term anticoagulation (extended after the initial and maintenance phases, generally after 3-6 months), provided the risk of bleeding is not high[20].
- There is a general consensus that positive DDi testing after anticoagulation is stopped identifies patients who have a high risk of recurrence and deserve extended anticoagulation. It remains a matter of debate whether persistently negative DDi results may safely be used to stop anticoagulation[21,22].
- It is not advisable to use DDi with this predictive scope in elderly subjects (>75 years old) because the levels are almost always increased in that population.
- Since males are at higher risk of recurrence than females, lower cut-off levels in men are suggested[23].

D-dimer in special populations:

- Pregnancy: the use of DDi in pregnancy is controversial; new approaches combining DDi and clinical scoring may improve PE diagnosis[24,25].
- Renal impairment: the DDi age-adjusted cut-off or the C-reactive protein-adjusted DDi testing in patients with severe renal dysfunction might be useful[26,27].

* For more information on COVID-19 in the haemostasis laboratory, please refer to the specific Focus series issue (ref. 301530; published by Stago)

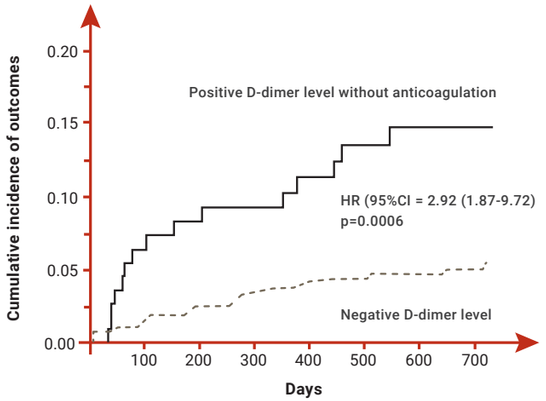
Figure 4. ***Kaplan-Meier cumulative recurrent rates of thrombosis in patients with positive DDi results who refused to resume anticoagulation (continuous line) or with persistently negative DDi results in whom anticoagulation was definitively stopped (dotted line). DDi level was measured one month after vitamin K antagonist treatment discontinuation (from Palareti et al.[30])***

Box 3

DDi testing in COVID-19 patients*

- DDi testing is recommended on admission (altered levels in one-third of patients) and every 2-3 days[28].
- VTE events are frequent; high DDi levels have been associated with VTE presence.
- Very high DDi levels (>3,300 ng/mL) in intensive care unit patients predict the presence of VTE complications[29].
- DDi level >5,000 ng/mL or baseline DDi level >2,000 ng/mL and increase of 100% within 24-48 hours are proposed cut-off values for therapeutic *versus* intermediate-dose prophylactic anticoagulation[21].
- DDi levels are negatively correlated with 28-day mortality[23].
- DDi levels >3,000 ng/mL are associated with 50-70% of non-survivors and 1-5% of survivors[28].

* Proposals as of the time of writing are informative and subject to change



Box 4

VTE recurrence risk prediction

"APIDULCIS" study procedure, based on serial DDi testing, to decide the duration of anticoagulation in patients after a first unprovoked VTE event (ClinicalTrials.gov Identifier NCT03678506)[31]:

- Apply the procedure only in subjects aged 18-75 years.
- Inform the patients about the scope and design of the procedure.
- Use sensitive, quantitative commercial assays, with gender-specific predefined cut-off levels for negative/positive results.
- Perform the first DDi assay during anticoagulant treatment.
- Continue anticoagulation if the result is positive.
- Stop anticoagulation if the result is negative.
- Repeat DDi testing after 15, 30 and 60 days.
- Resume anticoagulation (with low-dose Direct Oral Anticoagulants) immediately after the first positive DDi result.
- Consider stopping definitively anticoagulation if the serial DDi results are all negative.

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FIBRIN MONOMERS

- FRM directly related to fibrin formation are called soluble fibrin monomers (FM): when those monomers do not polymerize into fibrin to form a clot, they are in fact associated with other moieties into small complexes remaining therefore soluble; the range of their molecular masses is above the one of fibrin degradation products containing the DDi motif however.
- Fibrin implies the cleavage in fibrinogen molecule of at least one FPA (desA-fibrinogen).
- Plasma levels of FM are thus a reflection of active thrombin within the vasculature. Since their production does not depend on fibrinolysis by plasmin in contrast with DDi, they are often described as 'early' markers of *in vivo* coagulation activation.
- Below are some examples of clinical studies about FM. For a more comprehensive literature review, see Refaai M *et al.* Thromb Haemost 2018. Please note that the numerical values depend on the specific assay used in the study (for a general overview of FM clinical indications, see Table 1).

Thrombosis

Pulmonary embolism

In PE, using FM cut-off of value 3 *vs* 4 µg/mL showed sensitivity, specificity, and NPV of 100%, 33% and 100% *vs* 98.4%, 39.1%, and 98.3%, respectively. Thus, FM could exclude PE in 23% with the lower cut-off value and 27% with the higher cut-off value[32].

Deep vein thrombosis

Adding FM to DDi in patients with a high pre-test probability of DVT reduced the need for serial compression ultra-sonographies (CUS)[33].

Cardiovascular disease

FM were found to be significantly elevated in atrial fibrillation (23.2 *vs* 11.8 µg/mL; p=0.043)[34], in acute myocardial infarction (MI) during the first 24 hours *vs* >24 hours (p=0.003)[35], in MI patients who expired within 2 days *vs* survivals (p<0.001)[36], and in ST-elevated MI (STEMI) after enecteplase (p<0.001) and after percutaneous coronary intervention (PCI) (p=0.013)[37].

Ischaemic stroke

Higher FM were detected in acute ischemic stroke patients who presented 2-6 hours after symptom onset (p<0.01)[38]. In addition, FM predicted stroke recurrence as higher levels were detected in recurrent stroke (p<0.05). Further multivariate analysis linked FM levels with future recurrent event and/or death (95% CI. 1.04-2.18; p=0.036)[39].

Active cancer

In addition to DDi, FM were found to be significantly elevated in active cancer *vs* in remission status (p<0.001) and in expired *vs* survived patients (p=0.016)[40].

Intensive care unit patients

Disseminated intravascular coagulation

Studies found that average (+SD) FM level is significantly higher in patients who clinically developed DIC than the pre-DIC group (363±314 *vs* 181±132 µg/mL, p<0.01) and in overt *vs* non-overt DIC (55.6 *vs* 9.7 µg/mL; p<0.001)[41]. By multivariate analysis only FM could independently differentiate between overt DIC and non-DIC patients (OR 43.3; CI 4.6-406.7; p=0.001)[42].

Critically ill patients

Analysis of FM and DDi in critically ill patients (n=359) over six months follow up showed that FM is a better predictor of mortality in early stage DIC (p<0.001)[43]. For severely affected COVID-19 patients, its has been suggested that serial monitoring of FM could alert on the potential occurence of a macrothrombotic event in case of an abrupt rise[44,45].

ECMO

Over the first seven days after extracorporeal membrane oxygenation (ECMO) implantation in acute respiratory distress syndrome, including COVID-19 and non-COVID-19 patients, a drastic increase in FM levels (along with fribrinogen consumption) is observed, illustrating enhanced thrombin generation occurring despite continuous heparin infusion, resulting in fibrin formation[46].

Neonatal sepsis

In a pediatric study, FM were significantly higher in septic *vs* normal neonates (p<0.05) and in septic with DIC *vs* without DIC (p<0.001)[47].

In conclusion

Fibrin monomers (circulating as soluble complexes) are considered as early markers of *in vivo* coagulation activation (thrombin). Since their production does not depend on fibrinolysis by plasmin and since they do not diffuse into the extravascular space and cannot come from the latter in contrast with DDi, they have theoretically the potential to provide complementary information to the latter, which are widely available and used 24 hours a day. Moreover, there has been the concern that in case of 'fibrinolysis shutdown', such as in the sepsis setting, the production of DDi would be impaired and thus coagulation activation would be underappreciated. However so far, there are few hard data from clinical studies to support their use in clinical practice, but they deserve to be further investigated.

They share with DDi testing most of their limitations, such as complex mixture with heterogeneity, different assays with different monoclonal antibodies and epitopes, calibrators not amenable to full standardization, metabolic disposition modulating their rise in case of a burst of thrombin, influence of anticoagulation. In addition, the issue of artefactual production during blood sampling and plasma preparation should not be overlooked.

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Table 1. ***Main clinical indications of FM (results are expressed as in the article, according to the method of analysis).***
For a more comprehensive literature review, see Refaai M et al. Thromb Haemost 2018.

THROMBOSIS

Indication	Ref.	Topic	n	Key findings & conclusion
Pulmonary embolism	32	Peformance of FM for PE exclusion in symptomatic outpatients	426	Sensitivity : 92% Specificity : 73% *Similar performance as a reference ELISA DDi assay*
Deep vein thrombosis	33	Evaluation of the clinical performances of FM for the diagnosis of DVT in outpatients	464	In patients with abnormal DDi concentrations, irrespective of their pre-test probability score, the standard approach of serial ultrasound testing has a negative predictive value of 97%. Replacing the second ultrasound by a normal FM test leads to an equal negative predictive value. *A normal FM level might be able to replace the second ultrasound in patients with a normal first ultrasound.*

ACTIVE CANCER

Indication	Ref.	Topic	n	Key findings & conclusion
Outcome prediction	40	Predictive value of coagulation markers (including FM) for survival of cancer patients	268	Patients with active cancer had higher FM levels than patients in remission ($p<0.0001$) and non-survivors had higher FM levels than survivors ($p<0.0001$). *A single determination of FM is sufficient to strongly predict survival in cancer patients over the following 1 – 3 years.*

CARDIOVASCULAR DISEASE

Indication	Ref.	Topic	n	Key findings & conclusion
Atrial fibrillation	34	FM in acute stroke patients with atrial fibrillation	183	- FM level higher in patients with poor recovery (Barthel index <95) *vs* patients with good recovery ($p=0.002$) - FM level higher in atrial fibrillation *vs* non-atrial fibrillation patients ($p=0.043$)
Myocardial infarction	35	FM plasma level in acute myocardial infarction	47	FM superior for early diagnosis of myocardial infarction within 24 hours of onset as compared to DDi and CK-MB *FM are a useful marker of coronary thrombosis immediately before myocardial cell damage.*
	36	Predictive value of FM for mortality post myorcardial infarction	293	Non-survivors had significantly higher FM levels relative to survivors (day 2, $p<0.0001$). *Increased FM level is an independent predictor of mortality in patients with myocardial infarction. It allows further risk stratification when combined with known risk factors such as age and presence of congestive heart failure.*
	37	Effect of coronary reperfusion procedures on FM plasma concentration	38	FM concentration increased significantly following thrombolytic therapy and slightly increased after percutaneous coronary intervention (PCI).
Ischemic stroke	38	Kinetics of hemostatic abnormalities induced by acute ischemic stroke and thrombolytic (rtPA) or anticoagulant treatment (heparin)	44	FM increased within 1 hour after initiation of rtPA, peaked between 1 and 3 hours and declined toward baseline within 1 to 3 days. FM levels significantly increased at hours 1, 3 and 5 after initiation of heparin treatment. *The study revealed important similarities with hemostatic abnormalities induced by thrombolysis for myocardial infarction supporting a transfer of therapeutic concepts.*

INTENSIVE CARE

Indication	Ref.	Topic	n	Key findings & conclusion
Disseminated intravascular coagulation	41	Comparison of FM levels in DIC and pre-DIC patients *vs* controls	149	FM levels are higher in DIC patients than in pre-DIC patients ($p<0.01$) and in pre-DIC patients compared to controls ($p<0.01$). *FM could be the most useful marker for the diagnosis of DIC and pre-DIC.*

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Indication	Ref.	Topic	n	Key findings & conclusion
Disseminated intravascular coagulation *(cont.)*	42	Evaluation of the diagnostic performances of FM *vs* DDi in patients with overt and non-overt DIC	70	Median FM value in patients with overt DIC significantly higher than in non-overt DIC and non-DIC groups (p<0.0001; p<0.047). FM had higher sensitivity, specificity and negative predictive value than DDi to differentiate non-overt *vs* overt DIC. *FM are a better indicator than DDi in distinguishing patients with overt and non-overt DIC from non-DIC patients, raising the possibility for its diagnostic utility as a marker for impending overt DIC, aiding in early diagnosis and prompt therapeutic intervention.*
	43	Impact of using FM on prognostic performance of the ISTH DIC score	359	FM displayed the highest prognostic power *vs* DDi. *Selection of the fibrin-related marker as component of the DIC score has a small, but relevant impact on the prognostic performance of the overt DIC score.*
	48	Use of FRMs for the prediction of death at 30 days	779	*In patients with septic shock, FM are the FRM best related with late prognosis.*
Critically ill patients	46	ECMO-induced alterations in coagulation and fibrinolysis profiles in COVID-19 patients with acute respiratory distress syndrome	20	FM significantly increased from baseline to Day 7 (p<0.001). *Monitoring thrombin generation and fibrinlolysis may help predict bleeding complications in COVID-19 patients supported by ECMO.*
Neonatal sepsis	47	Early diagnosis of DIC in septic neonates	33	FM levels higher in septic neonates with overt DIC than in septic neonates without DIC (p<0.001) and higher in septic neonates *vs* controls (p<0.05). Sensitivity for DIC diagnosis: 100% Specificity: 93% Overall accuracy: 97.5% *High FM have a high positive predictive value for the early diagnosis of DIC in septic neonates.*

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Fibrin(ogen) Degradation Products

- FDP testing measures the breakdown products of fibrinogen and fibrin clot lysis by plasmin (Figure 5). FDP is a collective term for both fibrin and fibrinogen degradation products.
- Basically degradation of fibrinogen produces fragments D, E, X and Y .
- Although sites of plasmin-related proteolysis within fibrinogen are the same, products of fibrin degradation are different, and more diverse, than those of fibrinogen since (i) fibrinopeptides are removed, at least in part; (ii) fibrin is polymerized, ultimately covalently.
- FDP plasma levels give an indication of clotting and fibrinolytic activities *in vivo*[49].
- FDP assays are based on antibodies that detect epitopes on most of the degradation products.
- FDP assays do not distinguish between degradation products derived from fibrinogen or fibrin[50].
- The related assay provides a global and indistinct measure of FDP components, as opposed to DDi assays that provide selective measurement of compounds derived from cross-linked fibrin.

Consensus utility of FDP

- FDP is one of the parameters in the DIC diagnostic score from the International Society on Thrombosis and Haemostasis (ISTH) and Asian academic societies such as the Japanese Association of Acute Medicine (JAAM)[51].
- FDP may be used for monitoring of response to treatment of the underlying cause for DIC.
- As a standalone test, FDP lacks specificity for DIC as levels are increased in various other conditions (Table 2).

Other potential indications for FDP

- Assessment of the patient with suspected acute aortic dissection with raised levels supporting the diagnosis[52].
- Evaluation of the severity and prediction of outcomes in patients with COVID-19 infections. FDP may also have a role in the monitoring of response to anticoagulation therapy[53].
- Prognostication of certain cancers such as ovarian cancers[54].
- Evaluation of severity of placenta abruption[55].

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Table 2. ***Clinical conditions frequently associated with increased plasma levels of FDP and DDi***

Physiological states
- Elderly
- Pregnancy

Obstetric complicatons
- Intrauterine death
- Pre-eclampsia
- Abruptio placentae

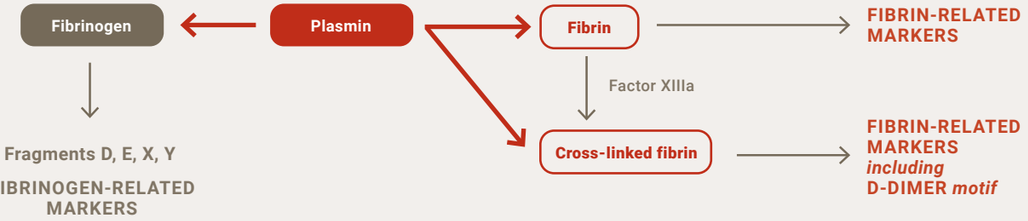
Inflammatory states
- Inflammatory disorders *e.g.* rheumatoid arthritis
- Hospitalized patients

Reduced clearance
- Severe liver disease including alcoholic liver disease
- Renal failure

Increased fibrinolysis with/without overt thrombosis
- Disseminated intravascular coagulation
- Arterial and venous thromboembolism
- Malignancies
- Acute promyelocytic leukemia
- Acute infections and sepsis
- Extensive burns
- Post-surgery
- Severe trauma
- Aneurysms
- Haematoma
- Envenomation (snake venoms)
- Thrombolytic therapy with tissue plasminogen activators

Note : the presence of rheumatoid factor and/or heterophilic antibodies may interfere with the test and cause spurious elevation of FRM levels

Figure 5. ***Proteolytic action of plasmin on fibrinogen, fibrin, cross-linked fibrin and its resultant products***
FDP assays measure most of these products (including DDi, degradation products of fibrinogen and fibrin), but not all, depending on assay-specific antibodies.



(should not be confused with fibrin-related markers)

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Fibrin-related markers - Terminology

- The term “fibrin-related markers” (FRM) refers to the moieties derived either from fibrinogen during fibrin formation or from fibrin and/or fibrinogen during their degradation by plasmin.
- FM (by definition, fibrinogen lacking at least one fibrinopeptide A (FPA) *i.e.* “desA(A)-fibrin”) are the FRM directly related to fibrin formation. Circulating so-called “soluble complexes” are made of at least one FM, non-covalently associated with one fibrinogen molecule, or related degradation products.
- D-dimer in short is used to refer to cross-linked fibrin degradation products containing the D-dimer motif.
- Of note fibrin(ogen) can be proteolyzed by other enzymes than plasmin, and by macrophages in case of fibrin deposits in the tissues.
- The acronym ‘FDP’ can be confusing since it can refer to both fibrin and fibrinogen degradation products.
  When specifically dealing with the former, it is wise to use ‘FnDP’.

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Diagnostics is in our blood.

I would like to dedicate the booklet to Guido Reber, whose vast knowledge on the complicated topic of FRM, and on many others, will miss me and likely many people who had the opportunity to meet him.

Thomas Lecompte

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ABBREVIATIONS

CUS: Compression ultrasonography

DDi: D-dimer

DIC: Disseminated intravascular coagulation

DVT: Deep vein thrombosis

ECMO: Extracorporeal membrane oxygenation

FDA: Food and drug administration

FDP: Fibrin and fibrinogen degradation products

FM: Fibrin monomer

FPA: Fibrinopeptide A

FPB: Fibrinopeptide B

FRM: Fibrin-related markers

ICU: Intensive care unit

MI: Myocardial infarction

PAI: Plasminogen activator inhibitor

PCI: Percutaneous coronary intervention

PE: Pulmonary embolism

PTP: Pre-test clinical probability

TAT: thrombin – antithrombin complex

tPA: Tissue plasminogen activator

ULN: Upper limit of the normal range

uPA: Urokinase plasminogen activator

VTE: Venous thromboembolism

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