Hemostasis Diagnostics

Focus
D3: D-Dimer Days

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Introduction

Since the start of the COVID-19 pandemic, healthcare systems are adjusting to the crisis all over the globe. In times of crisis, healthcare professionals are always looking for clear and practical ways to optimize processes to adapt to the sudden increase of patients requiring advanced care while at the same time trying to deliver the most appropriate care to improve patient outcomes.

Coagulopathy in patients affected by COVID-19 has been identified as a significant component of the evolution of severe cases. One marker of Fibrinolysis has garnered particularly the attention of healthcare professionals: D-Dimer. This molecule is a product of degradation of cross-linked fibrin and was identified as a marker that played a role in the monitoring and management of these patients.

D-Dimer is a well-established diagnostic tool in conjunction with a clinical pretest probability assessment model to exclude venous thromboembolism in patients suspected of deep vein thrombosis and pulmonary embolism. In addition to this intended use, D-Dimer is used as part of recommendations or has been identified as an important marker in many other conditions and that is why the D3:D-Dimer Days series was born.

This series aims to provide talks by eminent speakers in their field starting from a review of what was discovered over a period of a year following the COVID-19 outbreak related to the diagnosis and management of coagulopathy. The series then offers a general overview of Fibrinolysis, followed by a review of the analytical aspects of D-Dimer assays. Finally, over the last three talks the series covers the use of D-Dimer in clinical conditions like Cancer, Arterial diseases, and Sepsis.

Throughout this booklet you can find more details related to the speakers, their talks, some of the questions from the audience, the answers provided by the speakers, and all the links to be able to view or review the recordings.

Stay Safe and Take Care of Each Other
Werfen EEMEAI Hemostasis Team

Session 1

Covid19 Associated Coagulopathies: A Year in Review

In March 2020, the International Society of Thrombosis and Haemostasis (ISTH) published a guidance document aiming to provide a risk stratification for admission of a COVID-19 patient and for the management of coagulopathy which may develop in some of these patients, based on easily available laboratory parameters. The guidance lists four hemostasis markers (D-Dimer, Prothrombin Time, Platelet count and Fibrinogen, listed by order of importance) with D-Dimer as the most important one suggesting that a 3-4-fold increase in D-Dimer values may be considered a markedly raised D-Dimer.

Since then, several points have been raised related to the use of Coagulation Markers in the assessment of hemostatic anomalies, this topic is covered in this talk by Prof. Armando Tripodi. Additionally, several studies tried to assess the most appropriate treatment protocols to manage the coagulopathy and this topic is covered in this talk by Prof. Walter Ageno.

Speakers:

Prof. Armando Tripodi

Full Professor of Laboratory Medicine at Humanitas University.
Established Investigator, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, IRCCS Maggiore Hospital Foundation

Prof. Walter Ageno

Full Professor of Medicine at the University of Insubria
Director of the Short-Stay Medical Unit and Thrombosis Center

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Q&A Session 1

Covid19 Associated Coagulopathies: A Year in Review

Could you comment on the hemorrhagic complications and risk of bleeding in the COVID-19 population?

Based on what we know now, the increased risk of bleeding is as expected in the general population of acute medically ill patients. Those patients that are not admitted for COVID-19, we know that the use of low molecular weight heparin does increase, not significantly, but does increase a little bit the risk of bleeding, especially in older patients but the clinical benefit remains absolutely.

The first results that we do have on COVID-19 patients admitted to medical wards are pretty much in line with that. I would feel quite confident with regards to the ICU patients again, - as I mentioned, there isn't high risk of bleeding and we knew that before even for "non-COVID-19" patients - but we have to be very careful because these patients have usually low platelet counts and worsening renal function.

For this reason I definitely would stick with prophylactic doses unless higher doses are strongly indicated. The risk of bleeding, especially in ICU patients always needs to be carefully balanced. For the other patients I would use the same rules that we use for "non-COVID-19" and measure renal function. Also, pay attention to concomitant antiplatelet agents, of course.

Walter Ageno

Could you comment on the practice of prophylactic doses of low molecular weight heparin for moderate to high-risk patients being treated at home?

There are at least two or three trials trying to address this interesting topic. I'm sure about two there will be maybe a third one. This is certainly the most difficult population to enroll in a trial because these

patients are at home so you need help from the general practitioners, but this is a question that has never been completely answered even in the past. Of course, we do manage patients at home who may have the same risk factors as hospitalized patients and this is also true for COVID-19 patients. Some of these patients remain bedridden for many days with high fever and because of an acceptable respiratory function they remain at home, but their risk maybe increased.

The current guidance documents that I rapidly mentioned, do not suggest the routine use at home and I totally agree with that as there is no evidence to routinely use heparin at home. However, I take the responsibility, this is my opinion, to consider for some patients the possibility to use prophylactic doses, especially in those patients who do have additional risk factors, especially obese patients. Ideally these patients should have at least some laboratory tests done just to have information on the platelet count, renal function, coagulation if possible. That would be certainly safer, but I would not be against the use of LMWH at home in some high-risk patients.

Walter Ageno

Could you comment on the role of DOACs in COVID-19 patients either in Thromboprophylaxis or in the treatment of thrombotic complications?

I would like to give several answers related to this question. The first one is if the patient is already receiving oral anticoagulation, either with vitamin K antagonists or direct oral anticoagulants for other reasons, these patients need to stay on their drugs unless there is a contraindication and usually these contraindications come from the use of drugs that may interact with the direct oral anticoagulants for example.
In these cases, patients may be switched to low molecular weight heparin. But if no interference of the new treatments is expected, I definitely would suggest continuing with their anticoagulation drugs.

The second one is related to the treatment with direct oral anticoagulants of a Venous Thromboembolism that occurs during hospitalization. Also in this case this is absolutely a possibility. Again, just pay attention to potential contraindications which may be related to concomitant drugs that may interfere with the activity

of the direct oral anticoagulants or other contraindications that may come up, such as organ failure, but other than that, I would suggest the use of direct oral anticoagulants for the treatment of venous thromboembolism in these patients. For prophylaxis this is another issue. the first thing I would say that the direct oral anticoagulants are currently not approved for prophylaxis in medically ill patients in most countries. In some countries they are, for example, Betrixaban and Rivaroxaban are approved the United States. In Italy I could not use them just for the purpose of prophylaxis. However, there are some observational data on patients who have received some of the direct oral anticoagulants.

I have in mind a study published in Thrombosis and Hemostasis with Apixaban and its use was as safe and as effective as low molecular weight heparin, but this was an observational study with all its limitations to be considered.

Walter Ageno

From the laboratory standpoint the main issue here is that DOACs usually do not require Laboratory assessment to adjust the dosage as is for vitamin K antagonist and there are some reports in the literature that there may be some interference from, for instance, antiviral drugs on the blood concentration of DOAC. I think that at the moment, on one hand we should measure DOAC concentration in plasma to be sure that the expected concentration is there when the patient are treated with other drugs.
But on the other hand, even though we decided to measure the plasma concentration of DOAC at the moment we do not have established reference intervals, therapeutic intervals to be used in this patient because the literature is very scanty even in non-COVID-19 patients about the therapeutic interval as far as the concentration of DOAC is concerned.

I think that at the moment it's really very difficult and the laboratory cannot help unless we can define the therapeutic interval which is not established in reports from the literature or from the regulatory authorities. What we know at the moment is only the expected plasma concentrations which however are not connected with the clinical events in this patient. For the time being, I think that it's really very difficult to answer this question.

Armando Tripodi

Session 2

General Overview of Fibrinolysis

D-Dimer is one of the byproducts of Fibrinolysis, a process that breaks down blood clots to prevent them from growing and becoming problematic. The main enzyme involved in Fibrinolysis is Plasmin which cuts the fibrin mesh at various places, leading to the production of circulating fragments like D-Dimer that are cleared by other proteases or by the kidney and liver.

The process of Fibrinolysis however is much more complex and involves other actors like a few coagulation factors, tissue plasminogen activators, Plasminogen Activator inhibitors 1 & 2, α2-antiplasmin, and plasminogen among others. Additionally, fibrin and fibrinogen degradation by plasmin produces a heterogenous group of molecules called FDPs which include D-Dimer, but also Fibrin Monomers, and others. Please join us for the talk by Professor Colucci who provides a comprehensive overview of Fibrinolysis and its many aspects.

Speaker:

Prof. Mario Colucci

Professor at University of Bari "Aldo Moro",
Department of Biomedical Sciences and Human Oncology,
Bari, Italy

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Q&A Session 2

General Overview of Fibrinolysis

Could you share when testing for FXIII would be suitable?

While epidemiological investigations suggest that FXIII antigen, activity, and/or genotype may influence thrombosis risk (with considerable discordance among studies), FXIII assay in the clinical practice is recommended for identification of FXIII deficiency.

As part of Fibrin formation which clinical conditions would benefit from Fibrin monomer testing?

All conditions characterized by increased clotting activation, including VTE and DIC, would theoretically benefit from fibrin monomer (FM) testing, as FM represents an early and specific marker of fibrin formation. In septic patients, in particular, the combination of D-Dimer and fibrin monomer was shown to improve risk stratification over D-Dimer alone. However, while promising, FM assay presents several limitations (e.g., cut-off values, timing of FM measurement) and thus its place as prognostic marker for any given conditions needs to be validated by ad hoc prospective studies.

As a marker what information can Fibrin(ogen) Degradation Products provide to clinicians?

FDPs and D-Dimer are increased in many conditions and their meaning may change according to the specific condition. For example, we found that D-Dimer levels in sepsis correlated better with plasmin generation than with thrombin formation, which is the opposite of what happens in VTE patients.

Thus, due to the lack of specificity, the assay of FDPs, particularly D-Dimer, may provide valuable information to clinicians only in the well-known conditions for which the utility of the assay has been validated by clinical studies, namely VTE exclusion (in combination with clinical probability), DIC diagnosis (as part of DIC scores) and likely in determining the duration of anticoagulation.

Related to the Plasmin formation, could you explain the role of the different markers like PAI-1, plasminogen, alpha 2 antiplasmin, etc... in the laboratory evaluation?

Elevated levels of PAI-1 have been documented by a huge number of studies as a major mechanism of Fibrinolysis inhibition in many conditions associated with venous or arterial thrombosis, or DIC. Still, either PAI-1 nor t-PA is included in the panel of assays to assess thrombosis risk or prognosis (e.g., sepsis) likely because of the lack of standardization and reference values, methodological aspects, and other limitations. Concerning plasminogen and alpha2-antiplasmin, their assay in the clinical laboratory is indicated when a deficit of one these factors is suspected.

Related to Sepsis and the corrected D-Dimer, how should regular labs that are not able to perform the assay support clinicians in assessing these patients?

Our study on corrected DDimer is a proof of concept that adjustments for plasmin and thrombin generation might provide a better picture on what is going on in vivo. While encouraging, our data are insufficient to propose corrected DDimer as an alternative to currently used tests. Thus, regular labs should stick to the classical scores for DIC diagnosis and to clinical variables (SOFA, SAPS II).

Session 3

Analytical Aspects of D-Dimer Assays

D-Dimer molecules are generated through the degradation of cross-linked fibrin during Fibrinolysis and require the activity of thrombin, activated factor XIII (factor XIIIa), and plasmin. The action of Plasmin on the cross-linked fibrin clot results in the D-Dimer molecule. The D-Dimer assays have extensively been used and studied in the clinical management of Venous Thromboembolism for the exclusion of Deep Vein Thrombosis or Pulmonary Embolism using a test specific cut off value, units (D-Dimer Units or Fibrinogen Equivalent Unit), sensitivity, specificity, and negative predictive value.

D-Dimer can be tested on whole blood, plasma, or serum using antibodies that recognize a specific epitope on cross-linked D-Dimer molecules. There are many commercially available D-Dimer assays using either enzyme-linked immunosorbent assays (ELISA), immunofluorescent assays, latex agglutination assays or chemiluminescent assays. Each of these test methods differs in its limitations and interferences.

Laboratory assays are validated with standard, however, for D-Dimer the lack of such a single standard makes a direct comparison of different assays challenging. Since manufacturers use different antibodies that recognize different epitopes with varying kinetics, this makes the development of a universal standard for calibration a difficult project which makes standardization unlikely. Please join us for the talk by Miquel Sales who provides a comprehensive overview of the analytical aspects of D-Dimer Assays.

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Speaker: **Miquel Sales**

R&D Director, Assay Development Werfen

Q&A Session 3

Analytical Aspects of D-Dimer Assays

What are the studies required to obtain FDA exclusion claims?

The validation of the threshold of an assay for the exclusion of Venous Thromboembolism (VTE) (for both, Deep Venous Thrombosis (DVT) and Pulmonary Embolism (PE)) requires testing of VTE suspected patients in whom the diagnosis has been established or excluded using a defined diagnostic algorithm that includes a pre-test probability, D-Dimer testing and imaging techniques. For the population that has a final diagnosis of no VTE, it is also necessary to re-evaluate the patient after three months to confirm the negative diagnosis. These studies usually require thousands of patient samples tested in different institutions and countries. For details on these studies see CLSI H59-A (Quantitative D-Dimer for the Exclusion of Venous Thromboembolic Disease; Approved Guideline).

In VTE and PE, how should we choose our D-Dimer assay and supplier?

According to Professor Dempfle, the ideal D-Dimer assay should have some characteristics such as a long linearity, not affected by Fibrinogen and its degradation products, accessible 24/7, providing results in less than 15 minutes, and evaluated in appropriate clinical studies. According to him these goals are most easily achieved by automated latex-enhanced Turbidimetric Immunoassays (Dempfle C-E. D-Dimer testing and venous thromboembolism: four view points. J Thromb Haemost 2005; 3: 377–9). There are Turbidimetric assays in the market fulfilling these requirements.

What can you suggest to rule out the suspect of prozone effect (or hook effect) that may happen in the very high concentration of D-Dimer? Is there any standardized protocol to perform this evaluation?

Usually the D-Dimer assays, and in general all immunoassays, have some algorithms in the parameter settings of the instrument to identify this type of samples performing then automated dilutions of the sample.

I am not aware of any standard protocol to perform. However, if an inhibitory prozone is suspected a 1:2 or 1:4 sample dilution should help to clarify it. In case of inhibitory prozone the diluted samples after multiplying by the dilution, will produce a result higher than the undiluted sample. Be aware of the linearity and test ranges established for the assay so that the obtained values are well within them.

D-Dimer was recommended by scientific societies in the diagnosis and monitoring of COVID19, what is the impact of lack of standardization of the assay on the results we may obtain with different suppliers of the assay?

There is an association of D-Dimer with High risk of VTE and with a poor prognosis in COVID 19 patients. There is no standardization among D-Dimer assays and the threshold level established for one method is not transferrable to another one. Therefore, results should be interpreted within each individual assay.

Should there be a dedicated cut off for D-Dimer assays relative to COVID19 associated coagulopathy?

There are some publications giving cut off values to stratify the risk (Thrombosis Research 196 (2020) 318–321), but again the cut off should be established for each specific assay.

On several occasions, we observed some disagreements between suppliers, where one would be strongly positive and the other would be negative, what troubleshooting would you recommend in this situation?

D-Dimer results may be different among D-Dimer assays due to the specificity of the monoclonal antibodies used on each assay. As example of the difference between assays we could consider samples from patients with hyper fibrinolytic conditions or treated with profibrinolytic drugs.
In these patients the fibrinolytic fragment will be of a small size. D-Dimer assays with a preference for high molecular weight fibrin compounds will show lower levels of D-Dimer antigen than assays, which detect the D-Dimer epitope regardless of the molecular size of the fibrin compound.
There could be also some interference increasing or decreasing the patient sample result producing discrepancies in the comparison of different assays. As example there could be interferences produced by Rheumatoid factor or Heterophilic antibodies.

Session 4
D-Dimer in Cancer and VTE

Cancer-Associated Thrombosis (CAT) is an association that has been identified for quite some time even if all the mechanisms that induce thrombosis in cancer are still in the process of being fully understood. What is known is that the type of Cancer, its stage, any tumor-derived factors or genetics can all affect the thrombotic risk in cancer.

Cancer impacts all components of Virchow's triad Stasis through vascular compression and bed rest, Endothelial Damage by tumor vascular damage, and Hypercoagulability through the expression of procoagulant factors. In addition, cancer has some specific inflammatory actions that adds to the hypercoagulable state which makes Venous Thromboembolism the second cause of mortality in cancer patients.

To better evaluate the risk of thrombosis in Cancer patients, risk assessment tools were created and validated to calculate the risk of thrombosis in cancer patients. For example, the Khorana score is the most validated risk assessment tool in cancer patients and is validated primarily for outpatients and general cancer patients (i.e., solid tumors and lymphomas; not to be used for patients with brain tumors or myelomas) to predict thrombosis. Another example is the Vienna score which is a similar score but also includes measures of D-Dimer and soluble P-selectin (sP-selectin). Please join us for the talk by Professor Anna Falanga who provides a comprehensive overview of Cancer Associated Thrombosis.

Speaker:

Prof. Anna Falanga

MD, Professor of Hemalotogy at University of Milano-Bicocca, Director Department of Immunohematology and Transfusion Medicine, Director Hemostasis and Thrombosis Center at Hospital Papa Giovanni XXIII

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Q&A Session 4

D-Dimer in Cancer and VTE

When would you consider prophylactic anticoagulation for Cancer patients?

Thromboprophylaxis is not routinely recommended for all cancer patients. Though cancer patients are more likely than people without cancer to develop VTE, a number of cancer specific factors, such as the bleeding tendency at the site of the cancer, or a thrombocytopenia caused by chemotherapy can increase the bleeding risk in particular during anticoagulant treatment. Comprehensive management of VTE in patients with cancer includes both the identification of patients who are most likely to benefit from pharmacologic primary prophylaxis as well as the effective treatment to reduce the risk of VTE recurrence and mortality, as suggested by most international guidelines.

In hospitalized medical cancer patients, primary pharmacologic thromboprophylaxis should be offered, to all patients who have active malignancy, particularly in association with acute medical illness or reduced mobility, in the absence of bleeding or other contraindications.
To the same guise, in the setting of patients with cancer undergoing surgery, in particular those undergoing major surgical intervention, primary pharmacologic thromboprophylaxis is recommended with either unfractionated heparin (UFH) or LMWH unless contraindicated because of active bleeding, or high bleeding risk, or other contraindications. A combined regimen of pharmacologic and mechanical thromboprophylaxis may improve efficacy, especially in the highest-risk patients.

Concerning primary prophylaxis in ambulatory cancer patients undergoing anti-cancer drug treatments, who are the great majority of the cancer population, the decision is much more complex. Routine pharmacologic thromboprophylaxis is not indicated for all of them because the thrombotic risk is very variable among these individuals, depending on the type of cancer, the type of anti-cancer therapy, the stage of the disease, etc.
It is therefore very important, in this setting, to identify outpatients who are at 'high-risk' and can most benefit from antithrombotic prophylaxis, in whom the thrombotic risk outweighs the bleeding risk of anticoagulant drugs.

High-risk outpatients with cancer (Khorana score of 2 or more prior to starting a new systemic chemotherapy regimen) may be offered thromboprophylaxis with Apixaban, Rivaroxaban or low-molecular-weight heparins (LMWH) provided there are no significant risk factors for bleeding and no drug-drug interactions. Consideration of such therapy should be accompanied by a discussion with the patient about the relative benefits and harms, drug cost, and duration of prophylaxis in this setting.

Can regularly monitoring DD in high-risk cancer patients assist physicians in the management of their patients?

A single test is usually not sufficient to identify the level of VTE risk. Current guidelines suggest to classify patients as being at low, intermediate, or high risk for VTE based on validated risk assessment models (RAM) which include clinical risk factors and biological risk factors (i.e., Khorana score), and do not suggest to rely on only a single laboratory test. However, recent studies on patients with cancer-associated thrombosis (CAT), have identified D-Dimer as one of the laboratory biomarkers useful for the identification of patients at high thrombotic risk, in combination with clinical and biological variables of the Khorana score (Vienna-CAT, Pabinger 2009), or in combination with only one clinical variable, i.e. the tumor site (Pabinger 2018).

What markers would you recommend testing in a regular Lab that could assist in the assessment of endothelial damage in cancer patients?

Several proteins could be measured for evaluating endothelial damage because they are released by perturbed and/or activated endothelial cells, i.e.: soluble thrombomodulin, von Willebrand factor, E-selectin, t-PA, PAI, TFPI. Also the presence of circulating endothelial cells is a direct evidence of endothelial injury. Of interest, endothelial cells express different markers in different disease states reflecting the different mechanisms of endothelial injury.
However, most of these biomarkers are not routinely assessed by all laboratories, unless for research purposes. In this scenario the measurement of the vWF for assessment of endothelial damage is the most practical, as it is a diagnostic tool for specialized second level laboratories and therefore is more widely accessible.

Which risk assessment model would you recommend for institutions to implement in their organization, and which markers (if any)?

Risk assessment models can certainly help clinicians to select high-risk patients candidates to thrombo-prophylaxis, avoiding the use of anticoagulants in patients at low VTE risk. However, at present the available RAMs still have some limitations. Improvements in risk model rules have been made by modifications of the Khorana score, i.e. the PROTECHT, the CONKO and the Vienna-CATS scores, or by creation of a new score, i.e. the COMPASS-CAT. At this time, the best externally validated RAM remains the Khorana score, which also has the advantage of being composed by easily available variables.

In cancer patients treated with LMWH or UFH, when should anti-factor Xa activity be monitored?

LMWH are the reference molecule for the long-term treatment of venous thromboembolism (VTE) in cancer patients. The anti-factor Xa activity test is not routinely required in cancer patients treated with LMWH, but it may be suggested in particular cases i.e. renal insufficiency, obesity, weight <40 kg, thrombotic recurrence or active bleeding. In the case of UFH treatment, anticoagulant treatment monitoring is required, usually by APPT measurement, but also anti-Xa activity assay can be used.

Should thrombophilia studies be performed in patients with Cancer-Associated Thrombosis?

The influence of thrombophilia, such as Factor V Leiden, on the thrombotic risk of cancer patients has been shown. However, on a routine basis, it is not recommended to perform thrombophilic screening in these patients because in patients with cancer the risk of thrombosis due to cancer itself possibly outweighs the contribution of thrombophilic factors.

Session 5

D-Dimer and Arterial Diseases

Arterial diseases are a wide variety of conditions that can affect different organs. Coronary Artery Disease, which can lead to myocardial infarction, aortic aneurysms that can be complicated through a dissection, Ischemic stroke, mesenteric ischemia are all arterial diseases.

Thrombotic or bleeding complications of patients with arterial disease are a significant burden on healthcare systems and require a variety of diagnostic tool spanning from laboratory markers to imaging techniques that allow treating physician to predict or diagnose the disease to guide the best way to manage the patients.

Among the many markers that may play a role in the assessment and management of arterial diseases, the role of D-Dimer can play a role in assisting clinicians. Requesting the right marker for the right indication is always a challenge. Please join us for the talk by Professor Alessandro Squizzato who provides a comprehensive overview of the available literature and guidances that discuss when D-Dimer adds value and in which category of arterial diseases.

Speaker:

Prof. Alessandro Squizzato

Associate Professor at the Research Center on Thromboembolic Disorders and Antithrombotic Therapies, Department of Medicine and Surgery School of Medicine, University of Insubria

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Q&A Session 5

D-Dimer and Arterial Diseases

Could you share some information on Peripheral Artery Disease and the use of D-Dimer?

Peripheral arterial disease (PAD) is not an area I have extensive experience in. I did not find any relevant paper on the role of D-Dimer during an acute event (i.e. as SnOUT test). D-Dimer is certainly elevated in acute limb ischemia: however, the diagnosis is mainly based on symptoms and signs (i.e. 5 P of Pratt) associated with vascular imaging.

Kleinegris and colleagues reviewed the literature a few years ago with the aim to assess the value of D-Dimer as a predictor of arterial thrombotic events in patients with PAD. An increased D-Dimer appeared to be independently associated with a two times increased risk of near-term cardiovascular events (relative risk 2.30, 95% confidence interval 1.43–3.68). However, they concluded that, due to the extended heterogeneity of the included studies, cautious interpretation of these data is warranted. In 2020, Kremers and colleagues aimed to provide a comprehensive overview of biomarker testing in PAD as a first step to improve risk stratification. Forty-seven studies comprising 21 473 PAD patients met inclusion criteria and were included.

Patients with increased high-sensitivity CRP (C-reactive protein) levels had a relative risk of 1.86 (1.48-2.33) for major adverse cardiovascular events and a relative risk of 3.49 (2.35-5.19) for mortality. Increased fibrinogen and D-Dimer levels were associated with an increased relative risk of mortality of 2.08 (1.46-2.97) and 2.22 (1.24-3.98), respectively. Additionally, patients with increased NT-proBNP (N-terminal pro-B-type natriuretic peptide) and high-sensitivity cTnT (cardiac troponin T) levels were at an even higher risk of mortality with relative risks of 4.50 (2.98-6.81) and 3.33 (2.70-4.10), respectively.

In 2008, Vidula and colleagues found that among persons with PAD, circulating levels of D-Dimer and inflammatory markers are higher in the 1 to 2 years before death than in periods more remote from death. Increasing levels of D-Dimer and inflammatory biomarkers are independently associated with higher mortality in persons with PAD. More recently, McDermott and colleagues found that in PAD

patients with an ischemic heart disease event, D-Dimer was higher within 2 months of the event, compared to most values obtained 10 to 32 months previously. D-Dimer was also higher in cases as compared to controls during most visits within 8 months of the IHD event.

How should the emergency department approach D-Dimer as a marker as part of their triage/initial assessment of patients?

Many Emergency Department's (ED) patients with chest pain/dyspnea may have different explanations of their symptoms. I know that in many EDs it is a common clinical practice to test biomarkers, such as troponin, NTpro-BNP, and D-Dimer without assessing pretest probability of acute coronary syndrome, heart failure, and pulmonary embolism: even if testing biomarkers at admission is simpler and faster, this practice maybe increase the number of patients with a missed diagnosis and increase the number of tests inappropriately and uselessly requested (i.e. false negative and false positive results)

Is there a role for D-Dimer in the follow-up of patients with confirmed Arterial Thrombosis?

I am not aware of solid evidence on the usefulness of D-Dimer in the follow-up of patients with arterial thrombosis. However, I would discourage to use it as a stand-alone test to take any management decision. After a pulmonary embolism/deep vein thrombosis, D-Dimer may be useful to stop or continue anticoagulation 3 to 6 months after the acute event, but it is used with other parameters in a multiparametric assessment of risks and benefits. It is certainly recommended in DIC patients to evaluate, in combination with other hemostatic tests, the resolution or not of the thrombotic process during treatment of the underlying disorder.

Could you clarify the role D-Dimer in the diagnostic Algorithm of Acute Coronary Syndrome?

No guidelines suggest using D-Dimer when there is a suspicion of an acute coronary syndrome, and I would discourage using it. As I've shown in my presentation, ESC guidelines suggest using it - according to other published dedicated guidelines - in case there is also a concomitant suspicion of pulmonary embolism or aortic dissection, or when acute coronary syndrome has been excluded.

In patients with arterial diseases treated with LMWH or UFH, when should anti-factor Xa activity be monitored?

I would suggest the same recommendations as for venous thrombosis. UFH administration should be dosed according to aPTT levels; heparin levels measured as anti-factor Xa activity should be tested when patient has high levels of fibrinogen and/or factor VIII (during an acute phase reaction), aPTT is not sufficiently prolonged despite elevated (> 40.000 IU/day) doses of UFH, UFH is administered after a thrombolytic therapy, or when aPTT is already prolonged due to the presence of LAC, factor deficiency or presence of antibodies. For LMWH, anti-factor Xa activity should be tested in case of risk of inappropriate LMWH dosage, such as in patients with renal insufficiency, extreme body weights, pregnancy, neonates, children, or prolonged used.

When should thrombophilia studies be performed in patients with Arterial Thrombosis?

"Thrombophilia" has been developed and tested in patients with venous thrombosis: in particular, inherited factors have been discovered in families with recurrent thrombosis that occurred in young individuals. Arterial thrombosis is often caused by a local factor, i.e. atherosclerosis, and the role of the coagulation system is often less relevant than in venous thrombosis. In case of unexplained arterial thrombosis, it may be useful to perform some tests, in particular antiphospholipid antibodies (i.e. lupus anticoagulant, anticardiolipin antibodies, anti-beta2GPI antibodies) and homocysteine levels.
The role of other thrombophilia tests is marginal, and it is not useful to make treatment decisions.

Session 6

D-Dimer and Sepsis

Sepsis is a condition that rises from the body's response to infection by bacteria, viruses, or fungi and induces organ damage. It is one of the main causes of death in the ICU. In the process of clinical assessment of organ damage, tools like the sequential organ failure assessment score (SOFA score), or the quick SOFA score (qSOFA) assist health care providers in estimating the risk of morbidity and mortality due to sepsis.

Sepsis can evolve into disseminated intravascular coagulation (DIC) when the response to the infection becomes overwhelming and the involvement of coagulation and Fibrinolysis may aggravate the organ failure by generating clots throughout the vascular system.

The systemic activation of coagulation may lead to overconsumption of clotting factors and inhibitors and this imbalance of coagulation is associated with changes of the results of several coagulation markers like Prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, antithrombin and D-Dimer among others. Please join us for the talk by Dr. Mauro Panigada who provides a comprehensive overview of the role of D-Dimer in the diagnosis of Sepsis and its evolution.

Speaker:

Dr. Mauro Panigada

MD, Anaesthesia and Intensive Care at Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico | Policlinico Maggiore

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Q&A Session 6

D-Dimer and Sepsis

How do you differentiate DIC from other Thrombotic microangiopathies?

Basically, only platelets are activated in thrombotic microangiopaties, on the contrary all coagulation, Fibrinolysis and platelet systems are activated in DIC. For those who want to look further into this topic - suggested reading: https://rdcu.be/crAIx

For labs that don't have the option to evaluate a DDcorr what markers would you recommend testing to help with the evaluation of DIC?

To evaluate DIC I suggest complying with societies recommendations using the specific scores. For those who want to look further into this topic - suggested reading: DOI: 10.1111/jth.12155

Do you recommend regularly monitoring the lab tests for coagulation when managing a DIC Case?

Yes, I would recommend a regular monitoring of the lab test for a DIC case at least once per day.

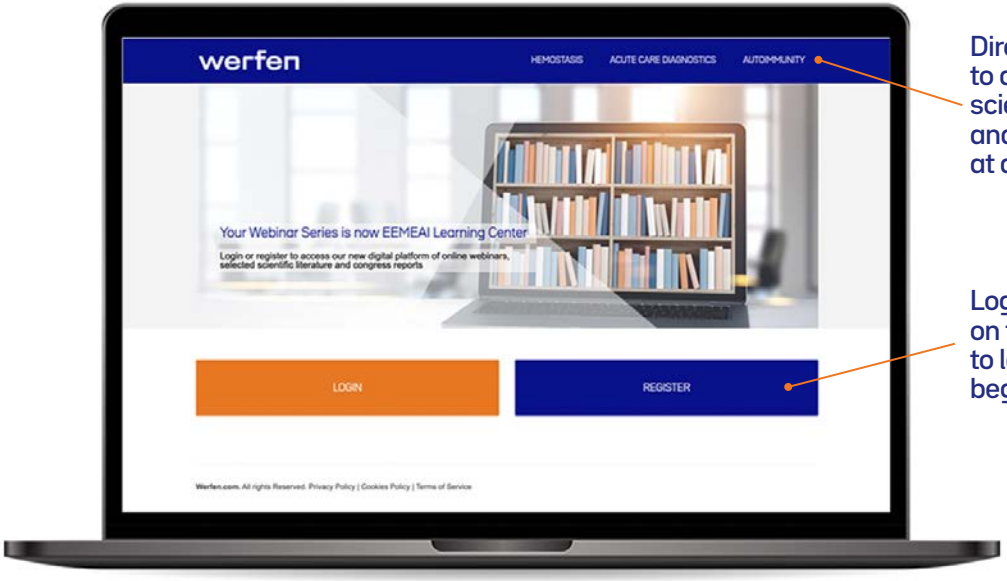
When do you recommend adding Antithrombin or Protein C measurements in the management of DIC?

I would recommend adding Protein C measurement when the clinical presentation of DIC is Purpura Fulminans. This is because it would lead to a specific treatment with Protein C supplementation.

The complete D3: D-Dimer Days Series is available on the **EEMEAI LEARNING CENTER**

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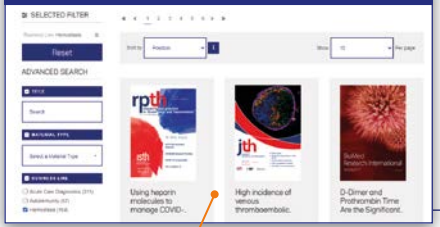
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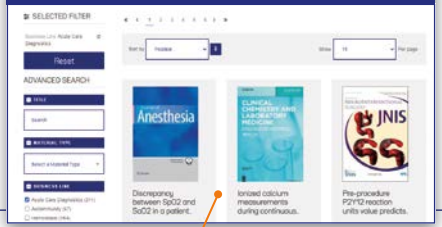


Hemostasis section:



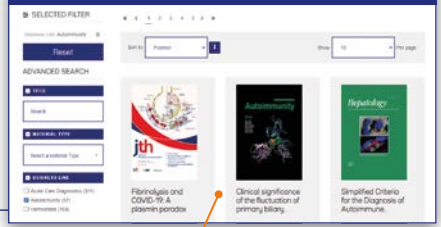
Content related to Hemostasis conditions like:
- Thrombotic Thombocytopenic Purpura
- Heparin Induced Thrombosis
- Anticoagulation monitoring
- Inherited Bleeding Disorders
- Thrombophilia and more...

Acute Care section:



Content related to Acute Care conditions like:
- Bleeding management
- Antiplatelet Therapy monitoring
- Blood Gas testing in Emergency Department, ICU, Operating Room, and Interventional Procedures

Autoimmunity section:



Content related to Autoimmune conditions like:
- Systemic Lupus Erythematosus
- Rheumatoid Arthritis
- Autoimmune Gastritis
- Antiphospholipid Syndrome
and many more...

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