Change of Guard in the EFLM Communication Committee (C-C)

by Giuseppe Lippi, EFLM Executive Board Secretary

Gratitude to MariaStella Graziani, outgoing C-C Chair.
MariaStella Graziani has decided to leave her third term of office as Chair of the EFLM Communication Committee ahead of time for personal reasons. During her term she has concentrated on expanding running projects as well as on establishing new relevant areas for Communication inside and outside the EFLM. The Communication Committee has gained a high profile and recognition through the work of recent years thanks to the efforts of Dr. Graziani. In particular, the efforts of the Committee have granted enormous success in developing visibility and collaboration with the EFLM member National Societies (NSs), strengthening and formalizing the relationships with industrial partners, developing visibility and collaboration with IFCC and IFCC Regional Federations, as well as promoting the profession, increasing awareness on the importance of clinical laboratories in healthcare and modern society and disseminating EFLM Newsletters among the many members of the EFLM NSs. During Dr. Graziani Chairship, the EFLM has considerably increased its visibility and acknowledgment throughout Europe. The Executive Board of EFLM is happy and honored that Dr. Graziani has taken over this task and wants to thank her for the valuable contribution in appreciation of the tremendous work that she has accomplished as chair of the Communication Committee throughout her terms of office. For her successor, Dr. Daniel Rajdl, MariaStella Graziani leaves a very good foundation where to start and build upon this groundwork. The EB of the EFLM wishes the best to Dr. Graziani for the rest of her outstanding scientific and professional career.

Introducing Dr. Daniel Rajdl, incoming new C-C Chair.
The EFLM Executive Board has appointed Dr. Daniel Rajdl as next Chair of the Communication Committee. Daniel is well-renew and esteemed within the EFLM, for having chaired the Working Group Distance Education and e-Learning for years and for having contributed to remarkably enhance the visibility and acknowledgment of EFLM Webinars in the past 4 years. The EFLM Executive Board is therefore confident that Daniel Rajdl will be a valuable and worthy successor to the former Chairs and will contribute fresh energy and new ideas along the fruitful and challenging path of his predecessor, Dr. MariaStella Graziani.

Laboratory diagnostic of venous thromboembolism : Where are D-dimer in 2019 ?

by François Mullier, Université catholique de Louvain, CHU UCL Namur, Namur Thrombosis and Hemostasis Center, Hematology Laboratory, Yvoir, Belgium

D-dimer is one of the most commonly requested coagulation tests. As a biomarker of activation of coagulation and fibrinolysis, D-dimer is mainly used for ruling out venous thromboembolism (VTE). The term D-dimer is a generic term comprising a broad mixture of plasmin-mediated degradation products of cross-linked fibrin, with molecular weights more likely to range from 190 to over 10,000 kDa. This heterogeneous composition, as well as the use of different monoclonal antibodies, lack of international certified internal control or calibrator, and different units, contribute to explain the dramatic inter-variability always found when comparing different D-dimer immunoassays.
This evidence emphasizes that further studied are urgently needed to reach a major degree of harmonization in D-dimer measurement, and constructive discussion among manufacturers, scientists and clinicians would be essential for achieving this goal. D-dimer fragments are mainly eliminated by renal clearance and by the reticulo-endothelial system. The plasma half-life of D-dimer is approximately 8h. Therefore, it is unadvisable, if not misleading, to repeat D-dimer testing within 8h after first test result. Pre-analytical requirements are paramount in the hemostasis laboratory, as well as in other areas of in vitro diagnostic testing. Although it may seem that the literature is quite reassuring concerning several preanalytical variables affecting D-measurement dimer (needle bore size, butterfly devices, use of pneumatic tube system, centrifugation, stability), this does not hold true. The main variables which could influence D-dimer measurement are venous stasis, hemolysis, clotting and inadequate sample volume. The tourniquet should never remain in place for more 1-2 min, to prevent spurious increase of D-dimer concentration. A recent study has shown that 17.1% of hemolyzed samples exceed the critical difference for D-dimer (65%). Even more importantly, such interference was not directly proportional to the degree of hemolysis, this making unreliable the use of correction formulas. The automatic assessment of hemolysis should be preferred over manual assessment, since the latter is affected by larger inter-individual variation. Currently, it is recommended to use D-dimer assays with a very high sensitivity (≥95%) and negative predictive value (NPV; ≥97%) to safety rule out venous thromboembolism (VTE). D-dimer shall also be measured with quantitative immunoassays, with an imprecision <10% at the diagnostic cut-off, displaying linearity between 50-5,000 µg/L Fibrinogen Equivalent Units (FEU). The use of POC D-dimer assays as a rapid screening tools is especially attractive for general practitioners (GPs), since central quantitative D-dimer assays are not always readily available. However, not all POC D-dimer assays can be reliably used for excluding VTE; only POC immunoassays which have been thoughtfully validated in clinical trials and cleared by the US Food and Drug Administration (FDA) or display the CE (European Community) mark shall be used. D-dimer may also be affected by using of two different measuring units: D-dimer units (DDU) or FEU. Results of D-dimer testing obtained with different methods should not be directly compared, nor used interchangeably. The cut-offs used by the laboratories for ruling out VTE should be validated in prospective studies and locally verified. A negative D-dimer value along with a low clinical probability (using clinical prediction rules) can safety exclude

VTE in suspected individuals. In rare situations, some patients with thrombosis may present with a false-negative D-dimer test results due to hypofibrinolytic state, small thrombi (i.e. distal deep vein thrombosis or isolated subsegmental pulmonary embolism), anticoagulant therapy or D-dimer testing performed to early or late after the thrombosis. A positive D-dimer value should always trigger additional imaging testing to confirm VTE, given that a wide array of diseases and conditions are characterized by non-specific increase of D-dimer values (i.e., aging, inflammation, cancer, renal failure). There are several available clinical prediction rules, and there is an ongoing trend towards simplifying these scores and encouraging their widespread use in emergency departments. For example, the use of simplified Geneva Score has similar efficiency and safety to the Geneva Score in excluding pulmonary embolism in association with D-dimer tests. The incidence of VTE is known to increase sharply with age, but also D-dimer values tend to increase with aging. More than 50% of older patients have D-dimer values higher than classical cut-offs. Therefore, a high rate of these patients with low clinical score would undergone unnecessary imaging testing. The use of age-adjusted cut-offs to safety rule out VTE have been proposed for increasing the predictive positive value (PPV) without significantly impairing the NPV, so ultimately improving the clinical usefulness of D-dimer measurement in elderly patients with low clinical probability. The following formula is the most frequently used: [age-adjusted cut-off, µg/L FEU] = [age, years]) x 10. Even though these adjusted cut-offs have been endorsed by several guidelines, a large number of laboratories are still not using them. Major efforts are hence needed for larger implementation of these recommendations. Another approach is to adjust the D-dimer cut-off according to the clinical probability (i.e., the so-called YEARS algorithm). The use of renal function-adjusted D-dimer is still not satisfactory. VTE exclusion in specific populations (i.e., pregnancy, heart failure, cancer, perioperative settings) is also challenging. Progress has recently been made for pregnancy. D-dimer levels increased physiologically in parallel with pregnancy, and persist elevated also in the postpartum period, until the 6th week. In suspicion of pulmonary embolism, since imaging tests may expose mother and the foetus to potentially unjustified radiation, the ability to rule-out pulmonary embolism using non-invasive testing becomes crucial. A recent multicenter prospective management outcome study, including 395 pregnant women with clinically suspected pulmonary embolism in the emergency department, showed that the rate of women in whom pulmonary embolism could be ruled out on the basis of a negative D-dimer result was clinically significant, thus avoiding chest imaging in 11.6% of cases. Notably, the rate of negative D-dimer test results decreased with increasing gestational age, but remained significant and clinically useful at least during the first and second trimesters (25% and 11%, respectively). More recently, pulmonary embolism could be safely ruled out by pregnancy-adapted YEARS diagnostic algorithm across all trimesters of pregnancy. CT pulmonary angiography could be avoided in 32-65% patients. D-dimer is also increasingly used within clinical decision models (mainly DASH, Vienna or HERDOO2 scores) for assessing the risk of VTE recurrence after a first unprovoked episode, and may also contribute to define optimal duration of anticoagulation treatment in patients with thrombosis. The risk of VTE is increased by 2-fold when D-dimer values are higher than the diagnostic cut-off after 3-months of anticoagulant therapy. Finally, D-dimer is systematically used for diagnosing of disseminated intravascular coagulation (DIC), and for screening medical patients at increased risk of VTE. Other emerging indications (i.e., prognostication of peripheral artery disease, screening of intracardiac thrombus) need further scrutiny.

REFERENCES

1. D-dimer: Preanalytical, analytical, postanalytical variables, and clinical applications.
   Favresse J, Lippi G, Roy PM, Chatelain B, Jacqmin H, Ten Cate H, Mullier F.
   Crit Rev Clin Lab Sc 2018 ;55:548-577.
2. A collaborative study by the Working Group on Hemostasis and Thrombosis of the Italian Society of Clinical Biochemistry and Clinical Molecular Biology (SIBioC) on the interference of haemolysis on five routine blood coagulation tests by evaluation of 269 paired haemolysed/non-haemolysed samples.
   Novelli C, Vidali M, Brando B, Morelli B, Andreani G, Arini M, Calzoni P, Giacomello R, Montaruli B, Muccini E, Papa A, Pradella P, Ruocco L, Siviero F, Viola FG, Zanchetta M, Zardo L, Lippi G.
   Biochem Med (Zagreb). 2018 Oct 15;28(3):030711.
3. Assessing clinical probability of pulmonary embolism: prospective validation of the simplified Geneva score.
   Robert-Ebadi H, Mostaguir K, Hovens MM, Kare M, Verschuren F, Girard P, Huisman MV, Moustafa F, Kamphuisen PW, Buller HR, Righini M, Le Gal G.
   J Thromb Haemost. 2017 Sep;15(9):1764-1769.
4. The diagnostic performance of renal function-adjusted D-dimer testing in individuals suspected of venous thromboembolism.
   Ten Cate V, Nagler M, Panova-Noeva M, Eggebrecht L, Arnold N, Lamparter H, Hermanns MI, Ten Cate H, Prins MH, Espinola-Klein C, Münzel T, Lackner KJ, Wild PS, Prochaska JH.
   Haematologica. 2019 Mar 14.
5. Diagnosis of Pulmonary Embolism During Pregnancy: A Multicenter Prospective Management Outcome Study.
   Righini M, Robert-Ebadi H, Elias A, Sanchez O, Le Moigne E, Schmidt J, Le Gall C, Cornuz J, Aujesky D, Roy PM, Chauleur C, Rutschmann OT, Poletti PA, Le Gal G; CT-PE-Pregnancy Group.
   Ann Intern Med. 2018 Dec 4;169(11):766-773.
6. Pregnancy-Adapted YEARS Algorithm for Diagnosis of Suspected Pulmonary Embolism.
   van der Pol LM, Tromeur C, Bistervels IM, Ni Ainle F, van Bemmel T, Bertoletti L, Couturaud F, van Dooren YPA, Elias A, Faber LM, Hofstee HMA, van der Hulle T, Kruip MJHA, Maignan M, Mairuhu ATA, Middeldorp S, Nijkeuter M, Roy PM, Sanchez O, Schmidt J, Ten Wolde M, Klok FA, Huisman MV; Artemis Study Investigators.
   N Engl J Med. 2019 Mar 21;380(12):1139-1149.
7. External validation of the DASH prediction rule: a retrospective cohort study.
   Tosetto A, Testa S, Martinelli I, Poli D, Cosmi B, Lodigiani C, Ageno W, De Stefano V, Falanga A, Nichele I, Paoletti O, Bucciarelli P, Antonucci E, Legnani C, Banfi E, Dentali F, Bartolomei F, Barcella L, Palareti G.
   J Thromb Haemost. 2017 Oct;15(10):1963-1970.