

## Preface

**Quality in Hemostasis and Thrombosis — Part III**Emmanuel J. Favaloro, PhD, FFSc (RCPA)<sup>1</sup> Giuseppe Lippi, MD<sup>2</sup> Mario Plebani, MD<sup>3</sup><sup>1</sup>Department of Haematology, Institute of Clinical Pathology and Medical Research (ICPMR), Westmead Hospital, Westmead, Australia<sup>2</sup>Laboratory of Clinical Chemistry and Hematology, Academic Hospital of Parma, Parma, Italy<sup>3</sup>Dipartimento Medicina di Laboratorio, Azienda Ospedaliera-Università di Padova, Padova, Italy

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Welcome to the latest issue of *Seminars in Thrombosis & Hemostasis*, the third to be devoted to the concept of “quality” within the field of thrombosis and hemostasis.<sup>1,2</sup> This series is intended to thoughtfully cover several clinical and laboratory issues related to diagnosis, management, and testing within the field of hemostasis/thrombosis, as well as to pursue genuine improvements whereby quality in healthcare can be considered an attitude that permeates entire organizations involved in patient care, which often extends beyond the boundaries of the laboratory.<sup>3,4</sup> Accordingly, we hope that this series promotes improvements in clinical, diagnostic, and therapeutic efforts to drive the best possible effects on patient outcomes related to bleeding and thrombotic disorders.

The current issue begins with a series of articles highlighted by two within-issue editorials.<sup>5–9</sup> This represents a new approach for this journal, but which may occasionally be employed as required. Typically, a synopsis of the issue’s contents is contained within the preface, but these particular articles have been additionally highlighted for reasons otherwise expanded within the editorials. The first editorial, by Othman and Emsley<sup>5</sup> discusses the significance of the work subsequently described by Woods and colleagues.<sup>6</sup> In brief, Woods et al<sup>6</sup> describe the identification of p.W246L as a novel mutation in the glycoprotein Ib  $\alpha$  (*GP1BA*) gene responsible for platelet-type von Willebrand disease (PT-VWD). PT-VWD and type 2B VWD both represent rare bleeding disorders characterized by increased ristocetin-induced platelet aggregation (RIPA) at low concentrations of ristocetin.<sup>10–13</sup> The diagnosis of these conditions is difficult and the differential diagnosis between them is especially challenging as evidenced by high levels of misdiagnosis of both conditions, but particularly PT-VWD. Five mutations in the *GP1BA* gene related to PT-VWD and less than 50 patients are currently reported worldwide. Woods et al<sup>6</sup> describe a male patient with severe

bleeding symptoms, macrothrombocytopenia, mild spontaneous platelet aggregation, positive RIPA at 0.3 and 0.4 mg/mL, von Willebrand factor (VWF) ristocetin cofactor (VWF:RCo) to antigen (VWF:Ag) ratio of <0.2, normal VWF propeptide (VWFpp) to VWF:Ag ratio, and RIPA mixing tests and cryoprecipitate challenge that were indicative of PT-VWD. To round off the diagnosis, the *GP1BA* gene was studied in the patient, in his mother, and in 100 healthy control subjects to identify a heterozygous substitution G > T located at nucleotide 3805 in the g.DNA of the patient’s *GP1BA* gene, resulting in a Trp to Leu amino acid change at residue 246 (p.W246L). This mutation was absent in his unaffected mother and also in the 100 controls and was predicted as damaging by in silico analysis. The residue W246 is located within the VWF binding region and exists in a strongly conserved position in the phylogenetic tree, which is expected to be unable to tolerate substitutions without changing its functional characteristics. These findings argue strongly in favor of the view that this substitution does not represent a polymorphism, and therefore, is responsible for the PT-VWD phenotype of the patient. The accompanying editorial by Othman and Emsley<sup>5</sup> highlights the importance of this new work, and it also extends the analysis of the proposed mutation by molecular modeling.

The second editorial,<sup>7</sup> along with the accompanying highlighted articles,<sup>8,9</sup> deal with recent initiatives in the standardization and harmonization of antiphospholipid antibody (aPL) testing, essential for the appropriate diagnosis and management of patients with antiphospholipid syndrome (APS) and other hypercoagulable states.<sup>14</sup> The leading issues in aPL testing include high vulnerability to preanalytical, analytical as well as postanalytical problems, the heterogeneous sensitivity of tests and reagents, high intermethod and interlaboratory variability, the clinically meaningful rate of false-negative and false-positive results, an absence of

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consensus for use of mixing tests, constraints around test availability in some geographic localities, and a well-known lack of compliance with current guidelines.<sup>15–29</sup>

We are currently at an important juncture in the improved development of standardization and harmonization of aPL assays. For lupus anticoagulants (LA) testing, three different testing guidelines have recently emerged.<sup>22–24</sup> These have been respectively developed by the LA Scientific Standardization Committee (SSC) of the International Society on Thrombosis and Hemostasis (ISTH),<sup>22</sup> the British Committee for Standards in Haematology (BCSH),<sup>23</sup> and the Clinical and Laboratory Standards Institute (CLSI).<sup>24</sup> LA comprise a class of aPL that show marked interference with *in vitro* phospholipid-dependent clotting tests, although paradoxically being associated with a kaleidoscope of thrombotic manifestations including recurrent venous and/or arterial thrombosis, as well as complications of pregnancy. Although there is agreement between several aspects of the three published guidelines, there are also notable differences. In his thorough comparative review, Moore essentially dissects the different guidelines for these elements of similarity and disparity.<sup>8</sup> For example, the ISTH recommendation to employ only dilute Russell's viper venom time (dRVVT) and activated partial thromboplastin time (aPTT) is not mirrored in the BCSH and CLSI documents. The potential for false-negatives in mixing tests is acknowledged by all panels, yet mixing tests remain mandated by ISTH as there are occasions when they are crucial to diagnostic accuracy. In contrast, BCSH indicates that a negative mixing test may not exclude the presence of a LA, and CLSI re-prioritizes the test order from the standard of "screen-mix-confirm" to "screen-confirm-mix," the latter (*mix*) being considered unnecessary in specific circumstances. Opinions also differ in the guidelines on setting cutoff levels. All guidelines cover testing of anti-coagulated patients, but substantially more detail is provided by CLSI. In total, although complete agreement is not apparent, the guidelines represent significant moves toward engendering common practices.

The situation for solid phase assays is different. These assays have largely developed from different manufacturers and research groups mostly independent of each other and thus with a reduced emphasis on "composite standardization." Indeed, there seems to be some manufacturer-related commercial benefit to having an assay that can be claimed to be "distinct" from (and by inference "better" than) their competitor products.<sup>29</sup> It is therefore both interesting and disturbing that the level of between laboratory or method variability in solid phase assays such as anticardiolipin (aCL) and anti- $\beta_2$  glycoprotein I (a $\beta_2$ GPI) antibodies is nearly an order of magnitude higher than LA assays.<sup>16,27,28</sup> This is somewhat counterintuitive as the solid phase assays inherently represent methods with theoretically lower variance, such as, enzyme-linked immunosorbent assays (ELISA), whereas the LA assays are based on clot-detection, historically known as highly variable assays. The report from Willis and colleagues<sup>9</sup> thus represents another important and concerted attempt to redress this deficiency in hemostasis diagnostics, describing various recent initiatives to improve standardization and harmonization in the area of solid phase aPL testing.

These initiatives have largely evolved from recent international congresses on aPL, such as those recently held in 2010 and 2013. For example, from the 2010 meeting, a task force comprising internationally recognized experts in the field of APS was formed to address these issues, and this resulted in several publications providing guidance and promoting standardization and harmonization of test methods and approaches.<sup>30,31</sup> Willis and colleagues<sup>9</sup> also highlight the importance of cutoff determination in aPL assays, along with the clinical significance of positive aPL results of varying magnitudes. This report will therefore hopefully advance the state of play in the area of APS diagnostics and builds on earlier attempts by others to drive standardization and harmonization in solid phase aPL testing.<sup>32–35</sup>

The next article in this issue of *Seminars in Thrombosis & Hemostasis* is by the guest editors to this issue and describes technological advances in the hemostasis laboratory.<sup>36</sup> Although automation is now commonplace in several areas of diagnostic testing, especially in clinical chemistry and immunochemistry, the concept of extending this process to hemostasis testing has only recently been advanced.<sup>37,38</sup> The main problems are the almost unique biological matrix (i.e., citrated plasma, which can only be used for clotting assays and few other notable exceptions), and the highly specific pretreatment of samples, which is particularly distinct to other test systems. Nevertheless, automation is now starting to embrace hemostasis testing, with the more relevant developments including the growing integration of routine hemostasis analyzers with track line systems and work cells, the development of specific instrumentation tools to enhance reliability of testing (i.e., signal detection with different technologies to increase test panels, plasma indices for preanalytical check of some interfering substances, failure patterns sensors for identifying insufficient volume, clots or bubbles, cap piercing for enhancing operator safety, automatic reflex testing, automatic re-dilution of samples and laser barcode readers), preanalytical features (e.g., positive identification, automatic systems for tube(s) labeling, transillumination devices for reducing venous stasis), and postphlebotomy tools (pneumatic tube systems for reducing turnaround time, sample transport boxes for ensuring stability of specimens, monitoring systems for identifying unsuitable conditions of transport). However, coagulation/hemostasis testing still requires specific technical and clinical expertise, not only in terms of measurement procedures but also for interpreting and then appropriately utilizing the derived information. Thus, additional and special caution has to be used when designing projects of automation that include coagulation/hemostasis testing, since peculiar and particular requirements must be taken into account.

The next chapter is by Malar and colleagues,<sup>39</sup> who provide a useful overview of the requirements for validation of hemostasis assays, given that the clinical hemostasis laboratory is a complex testing arena and employs many different tests using a wide assay of methodologies, where results are expressed in a broad variety of unique units (concentration, activity, time, percentage, ratio). As there are few established international standards, many of the

related reference values are derived from a local plasma pool or manufacturer's standards, and several other issues complicate the validation and performance of coagulation testing. Before an assay can be introduced into clinical use, both analytical and clinical performance parameters must be validated or verified using acceptable standard validation procedures. This article provides a valuable guide to, and several recommendations for, the test evaluation and validation process.

Next is an article from Kandice Marchant<sup>40</sup> on algorithmic approaches to hemostasis testing. Given the complexities and unique issues related to hemostasis testing (as partially identified in the previous articles in this issue), there is considerable clinical value to be gained from specific input from hemostasis experts to help interpret test findings, and then guide requirements and recommendations for further investigation. This is more so evident given the rapidly expanding knowledge of both bleeding and thrombotic disorders, an ever-widening test menu, the significant sensitivity that hemostasis testing has to many preanalytical issues (e.g., hemolysis, fill volume, time, temperature, storage conditions), and the interference in test results of many commonly prescribed drugs. In this article, the important role that pathologists serve in evaluation of a patient for a bleeding or thrombotic disorder is specifically outlined. In particular, hemostasis testing can proceed in a logical fashion by using predefined algorithms and be reported using patient-specific comments that take into account clinical history and medication therapy. This approach can lead to improvements in the diagnostic process, prevent misdiagnoses, and also lead to improved utilization of laboratory resources and a decreased time to disease diagnosis.

Craig Thelwell<sup>41</sup> then overviews biological standards for potency assignment to fibrinolytic agents used in thrombolytic therapy. Thrombolytic drugs are used for the treatment of many thrombotic disorders.<sup>42–46</sup> These include acute myocardial infarction, acute ischemic stroke, and pulmonary embolism. Before their use, biological standards are used for their potency assignment. Although current approaches ensure the consistency of drug dosing, the emergence of generic biosimilar products and new recombinant variants, where functional differences impact on the relative biological activity in different assay systems, may pose future challenges and may require a more demanding system of standardization.

The influence of diet and nutrients on platelet function is then extensively reviewed by Bradley McEwen,<sup>47</sup> one of our previous Eberhard F. Mammen Young Investigator Awardees.<sup>48</sup> Platelet activation and aggregation play an integral role in hemostasis and thrombosis, and diet and nutrients actively participate to modify cardiovascular disease (CVD) progression, which otherwise is recognized to be the leading cause of death worldwide. Dietary habits, such as, the Mediterranean diet which is high in omega-3 polyunsaturated fatty acids (PUFA) and vegetarian diets have inverse relationships with CVD. Diet and nutrients can also modulate platelet function and other hemostasis pathways, and therefore, they also have the potential of altering test findings using platelet

function tests. For example, dark chocolate, foods with low glycemic index, garlic, ginger, omega-3 PUFA, onion, purple grape juice, tomato, and wine all reduce platelet aggregation, and dark chocolate and omega-3 PUFA also reduce P-selectin expression. In addition, dark chocolate reduces procaspase-activating compound 1 (PAC-1) binding and platelet microparticle formation, berries inhibit platelet function, energy drinks increase platelet aggregation, and caffeine increases platelet microparticle formation, which is now extensively recognized to represent prothrombotic conditions. Therefore, repeat testing of platelet function testing may be required, not only after exclusion of known antiplatelet medications, but also potentially after exclusion of dietary substances/nutrients that could have plausibly affected initial test data.

The quality of transfusion products in blood banking is then extensively discussed in the next article from Franchini et al.<sup>49</sup> A primary goal in therapeutic medicine is to promote high standards of quality and to produce ever safer and more efficacious products, and this is certainly true of transfusion medicine and associated cellular therapies. The establishment of a transfusion service quality management system, which includes several organizational structures, responsibilities, policies, processes, procedures, and resources, is now mandatory and widely regulated worldwide. In this review, the authors summarize the current knowledge on the quality system in transfusion medicine as applied to the production of blood components, including red blood cells, platelets, and fresh frozen plasma.

The remaining series of articles in this issue relate to various external quality assessment (EQA) studies in hemostasis. The lead article by Hsu et al<sup>50</sup> analyzes data from the External Quality Control of diagnostic Assays and Tests (ECAT) program to assess current international clinical laboratory practice and performance of different methods for factor XIII (FXIII) testing. A total of 1,283 results from surveys conducted in 2010 and 2011 were assessed, comparing the three available methods for detecting FXIII deficiency, namely clot-solubility qualitative activity, quantitative activity, and antigen. Clot-solubility qualitative assays detected a deficiency in only 16% (11/69) of samples with less than 2% FXIII, with assays using added thrombin detecting more deficiencies (33%) than assays without added thrombin (11%). The most commonly used quantitative activity method tended to produce higher results for low FXIII samples than other quantitative activity methods, whereas antigen assays generally showed best accuracy at low levels. Interlaboratory imprecision evidenced wide interlaboratory variability, especially for samples with less than 10% FXIII activity. Laboratory interpretation of test results (as *normal* vs. *abnormal*) was good, especially for specimens with  $\leq 25\%$  FXIII compared with specimens with 26 to 70% or those with  $>70\%$  FXIII. The authors conclude that quantitative activity assays perform better for detecting FXIII deficiency than clot solubility assays, although some quantitative activity assays overestimate low factor XIII levels.

The next article by Favaloro and Bonar<sup>51</sup> reports on EQA/proficiency testing, as well as internal quality control (IQC), for the most common platelet function screening instrument, the PFA-100 and its upgrade model the PFA-200.

Platelet function testing is an essential component of comprehensive hemostasis evaluation within the framework of bleeding and/or bruising investigations and it may also be performed to evaluate antiplatelet medication effects.<sup>52</sup> The PFA-100/200 is sensitive to a wide range of primary hemostasis-related disorders, including platelet function defects and von Willebrand disease (VWD), as well as to some antiplatelet medications.<sup>53</sup> EQA, proficiency testing, and IQC are critical to ensure quality of test practice, inclusive of all hemostasis tests.<sup>54</sup> However, EQA and IQC for platelet function testing, including the PFA-100, is logistically challenging, given theoretical requirements for production, storage, and shipment of large volumes of “stabilized” normal and pathological blood/platelets covering both normal function plus a wide variety of potential defects.<sup>55</sup> Thus, platelet function tests, despite having been performed by most hemostasis laboratories for decades, are poorly standardized, with EQA and IQC processes at their relative infancy. Favaloro and Bonar describe the interesting development and testing of novel feasible approaches to both EQA and IQC of PFA-100/200 instruments, whereby a range of formulated “platelet function antagonist” materials are used. The study findings not only support the concept that EQA/IQC is possible for platelet function testing but also provide a valuable mechanism for monitoring and improving laboratory performance in this area. For EQA purposes, “challenge material” is distributed to participants of the RCPAQAP (Royal College of Pathologists of Australasia Quality Assurance Program) and citrated normal whole blood collected on site is then added locally, thereby creating test material that can be locally evaluated. Several exercises have been conducted over the past 6 years, tested in 26 to 50 laboratories depending on the year of dispatch, and comprising a total of 26 challenges, with most designed to mimic moderate to severe primary hemostasis defects. Both numerical results for PFA-100/200 closure times (CTs) and interpretive comments supplied by participants are analyzed. In summary, reported CTs for each challenge were within limits of expectation and good reproducibility was evidenced by repeated challenges. Coefficients of variation (CVs) generated for challenges using the two major PFA-100/200 cartridge types (Col/ADP and Col/Epi) are always similar to those obtained using native whole blood, and in general, range from 15 to 25%. Interpretations were also in general consistent with expectations and test data provided by laboratories. The EQA created material has also been assessed within the context of possible IQC material. This report provides an essential update to earlier reports from this group of workers.<sup>55–58</sup>

Smock and colleagues<sup>59</sup> then address the diagnostically contentious area of heparin-induced thrombocytopenia (HIT), in particular, focusing on proficiency test results from North America and the NASCOLA (North American Specialized Coagulation Laboratory Association) group. Five proficiency testing challenges comprising 10 samples (3 positive, 2 weak positive, and 5 negative) were distributed in 2010–2012 to evaluate laboratory testing for HIT and a total of 355 results were submitted from 43 laboratories. Most test results derived from commercial ELISA methods, predomi-

nantly polyvalent assays, and laboratories performed well in the classification of clear negative and positive samples. Thus, 100% of results submitted for the five negative samples ( $n = 173$ ) and 97% of immunologic results submitted for the three positive samples ( $n = 105$ ) were correctly classified. However, there was some difficulty in the classification of the two weak positive samples ( $n = 70$ ), where, in one survey, 61% of results were classified as positive, 21% were called negative, 16% were called borderline, and 2% were called inconclusive. In a second survey, 16% of results were called positive, 56% were called negative, and 28% were called borderline. Significant interlaboratory variation was also observed for ELISA results, with CVs of ~20 to 30%.

The final article in this issue by Perry et al<sup>60</sup> is on EQA for the molecular genetic analysis of hemophilia and other heritable bleeding disorders, otherwise recognized to be frequently requested laboratory investigations, but generally neither well-standardized nor externally assessed. The UK National External Quality Assessment Scheme (UK NEQAS) for heritable bleeding disorders was established in its current format in 2003, and currently, has 27 registered participants in the United Kingdom, the European Union (EU), and non-EU countries. Two exercises per year are circulated to participants, comprising either whole blood or DNA isolated from cell lines, and laboratories asked to analyze the samples and generate a report, which is then assessed by a panel comprising clinicians and scientists with expertise in this area. Samples to date have involved analysis of the *F8* gene [10 exercises], the *F9* gene [4 exercises] and the *VWF* gene [3 exercises], entailing a wide spectrum of mutations that represent the routine workload encountered in the molecular genetics laboratory. The majority of laboratories in each exercise passed, but a small number did not. Reasons for failing include clerical errors, genotyping inaccuracies, and failures to correctly interpret data. Overall, the authors have observed an improvement in quality of reports submitted for assessment, which is therefore of additional value to referring clinicians and counselors.

The rest of this issue contains some correspondence related to previous articles published in *Seminars in Thrombosis & Hemostasis*.<sup>61–66</sup> As usual, we wish to thank all the authors to this issue for their unique and comprehensive contributions and hope that our readership will find interest in the contents.

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