Preface

Recent Advances in Thrombosis and Hemostasis – Part III

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Beauty is in the eye of the beholder

In Molly Brown by Margaret Wolfe Hungerford, 1878

The idiom, in similar wording, actually originates from the old Greek philosophers. This idiom is often used today to illustrate any experience or perception that is subjective and personal. The main aim of *Seminars in Thrombosis and Hemostasis* is to publish reviews, driven by topics related to the themes of 'thrombosis' or 'hemostasis.' Nevertheless, original peer reviewed research papers are also published in this journal. It should be recognized that differences exist between personal opinions on the proportion of original papers *vs* reviews that should be published in this journal, and differences may also exist in personal perceptions of what actually constitutes a "review." In this third part of the 'Recent Advances in Thrombosis and Hemostasis' series, the proportion of original articles may seem relatively high for what is primarily seen as a review journal. In the humble opinion of the editor of this issue, of the 10 contributions to this issue, 3 are purely original research, 2 are a combination of original research and literature reviews, 3 are review articles, and 2 are systematic reviews and meta-analyses. The latter articles become particularly problematic to characterize specifically as original papers *or* reviews, since they are definitely reviews of the literature and probably more complete than regular review articles, and given they are based on extensive literature searches according to a predefined protocol. On the other hand, they do contain original analyses of the data. However, even a regular review article will contain a Discussion section, where the author makes a less formal, but still personal and hopefully original (or else it could be plagiarism) synthesis of the data reviewed. Thus, it seems logical to acknowledge the systematic reviews as part of the review article 'count' for this issue.

This issue starts with three articles on the epidemiology of venous thromboembolism (VTE). Deficiency of antithrombin is the hereditary thrombophilic defect with the highest risk for VTE.[1] In a systematic review and meta-analysis, Croles et al have quantified the risk of first VTE and of recurrence in patients with congenital antithrombin deficiency, and their results inform us of the need for indefinite duration of anticoagulation when they have suffered an episode of VTE.[2] Moving on to the acquired risk factors, it is well established that long-distance travel by plane is associated with an increased risk of VTE, albeit small in absolute numbers.[3] The risk is higher for long-haul flights than for long-distance surface travel.[3] Lippi and Favaloro are herein specifically addressing the risk associated with travel by car, by reviewing available studies and case reports.[4] The risk is not as clear cut as for travel by plane, but the authors end up with suggestions for VTE prevention, particularly for travelers with additional risk factors. The last epidemiological contribution addresses the risk of pulmonary embolism (PE) after surgery for lung cancer, both of which are established risk factors. In a retrospective cohort study, Li et al analyzed the risk for PE and for fatal PE and independent risk factors for PE.[5] Although the overall 30-day event rate of PE without prophylaxis is not impressive (0.57%), the results indicate that in the presence of particularly stage IV of lung cancer, with or without extensive surgery, extension of prophylaxis up to a month should be considered.

The characteristics of deep vein thrombosis (DVT) can be associated with outcomes such as recurrence and mortality. We accept that unprovoked DVT as well as proximal DVT are associated with a higher risk of recurrence than provoked or distal DVT, respectively. Bikdeli et al have now analyzed outcomes in relation to the side of the DVT, utilizing data from the Registro Informatizado Enfermedad TromboEmbólica (RIETE) database.[6] Over 30,000 patients were included in this analysis. Whereas differences in outcomes between DVT in the right or left leg are not sufficiently large to warrant different management, the few patients diagnosed with bilateral DVT have more comorbidities and higher risk for PE within 90 days and death within 1 year, justifying special attention in their management.

The next six contributions to this issue deal with treatment with oral anticoagulants. Any anticoagulant therapy is associated with an increased risk of bleeding. Whereas we will hardly ever abstain from anticoagulant treatment of a newly diagnosed VTE, unless there is active bleeding and a vena cava filter is inserted, we may want to discontinue

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treatment after the minimum duration considered acceptable. To this extent, a risk assessment model can be helpful. The Hypertension, Abnormal Renal/Liver Function, Stroke, *Bleeding* History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly (HAS-BLED) score was developed and validated in patients with anticoagulation for stroke prophylaxis in atrial fibrillation.[7] Rief et al explored its performance in a prospective cohort study of patients with VTE.[8] Their results indicate that a HAS-BLED score of 3 or higher could be helpful in identifying patients at high risk of major bleeding, and it seemed to perform better than the recently published VTE-bleed score.[9]

Non-vitamin K antagonist oral anticoagulants (NOACs) were studied well in large phase III trials that addressed efficacy and safety in general, but several subsets of patients were excluded. Individuals with end-stage renal disease were not included, but based on pharmacokinetic modeling, there is in some jurisdictions now an expansion of the indications to these patients. Klil-Drori and Tagalakis are herein reviewing existing data on warfarin and different NOACs for this patient population.[10] Interestingly, they find that the commonly used warfarin is probably less safe than some of the NOACs for these patients. Mechanical heart valves are still considered a contraindication for NOACs based on the RE-ALIGN study with dabigatran that was prematurely stopped for safety.[11] For patients with bioprosthetic heart valves, the situation is different, since they do not require vitamin K antagonists, at least not for long-term prophylaxis against stroke. Russo et al describe the outcomes of 122 patients in their database that had the combination of atrial fibrillation, bioprosthetic heart valve or valve repair, and NOAC treatment.[12] They also review the literature and conclude that existing evidence does not support the exclusion of these patients from use of NOACs. In the following article, they perform a similar analysis of patients with atrial fibrillation, cancer, and treatment with NOACs and report very good efficacy in 76 patients.[13] Data from the recently published Hokusai VTE Cancer study also demonstrated good efficacy of the NOAC edoxaban, in fact not inferior to that of low-molecular-weight heparin, but with an increased risk of major bleeding, especially among patients with gastrointestinal or urothelial cancer.[14] This may also pertain to the population with atrial fibrillation. A systematic review and meta-analysis demonstrated a 10% reduction in all-cause mortality with NOACs compared with warfarin, which was related to both a reduction in fatal bleeding and lower cardiovascular mortality.[15] Gomez-Outes et al have here looked further into the causes of death in the NOAC trials in the VTE-population in systematic review and meta-analysis.[16] The leading cause of death was cancer without a difference between NOACs and vitamin K antagonists. Continuing on the cancer theme, Tufano et al have reviewed the dilemmas that face the clinician when ordering both chemotherapy for cancer and anticoagulation in atrial fibrillation.[17] Cardiotoxicity and optimal choice of antiarrhythmic agents, chemotherapy-induced liver dysfunction or thrombocytopenia, and sometimes renal failure will definitely require a multidisciplinary approach.

This issue ends with three Letters to the Editor, (1) discussing the optimal timing of the vital signs measurement for best risk stratification of PE using the simplified PE Severity Index,[18] (2) demonstrating a streamlined algorithm for treatment of VTE and its evaluation at Oregon Health & Science University,[19] and (3) a report on a patient with afibrinogenemia and both bleeding and thrombotic manifestations, eventually refractory to dual antiplatelet therapy and fibrinogen replacement but successfully treated with the protease activated receptor 1 antagonist vorapaxar.[20]

This compilation contains many exciting presentations of the recent advances in our field and should provide useful reading for many clinicians in our field. I hope you will enjoy this mixture of reviews, systematic reviews and meta-analyses, original articles, and letters.

Conflict of Interest
None.

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