

Preface

Recent Advances in Thrombosis and Hemostasis—Part IX

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It is difficult to make predictions, especially about the future.—

Attributed to many:

Niels Bohr, quantum physicist, 1885–1962

Yogi Berra, baseball player and philosopher, 1925–2015

Questions are often raised whether one should use the term “risk factor” or “predictor,” and sometimes they are used interchangeably. The general opinion is that “risk factor” is a broader term and poorly defined, to the extent that many epidemiologists recommend avoiding it.¹ In this compilation issue, we have three contributions that use the term “risk factor(s),” one that uses “predictor,” and another one with the similar term “predictive score.” If we had an epidemiologist as the Guest Editor for this issue, maybe the authors of the manuscripts using “risk factor” would have been criticized. I have restricted my general critique regarding the statistics and epidemiology to some better-defined areas. First, we see many submissions with *p*-values and proportion numbers containing too many active digits. When the denominator, for example, is less than 100, there is no point providing a proportion of 59.9% or a *p*-value of 0.0376. That will give a false impression of very high precision, which is not possible with such a small denominator. The results have to be rounded off. Some journals will not accept more than one active digit for *p*-values that are nonsignificant; for example, *p* = 0.44 must be rounded off to 0.4, since the result will not be more nonsignificant by adding digits. Second, distributions of data need to be checked for normality, so that skewed distributions are reported with median and interquartile range (or range) and analyzed with the appropriate test. Third, the term “multivariate” is often wrongly used. When we are analyzing different variables and testing which one(s) might be independent for an outcome, we should use “multivariable.” On the other hand, “multivariate” is used when we analyze more than one outcome.

Let us now take a look at the contributions to this issue of *Seminars in Thrombosis and Hemostasis*, starting with some studies focusing on predictors. In patients with dilated cardiomyopathy, there is reduced wall motion and thereby a tendency to blood stasis in the left ventricle. A substantial minority of those patients develop a mural thrombus, with subsequent risk for embolization and stroke. Wu and colleagues reviewed retrospectively 3,134 patients with dilated cardiomyopathy and found that among 15 different variables, elevated D-dimer and reduced ejection fraction appeared to be independent risk factors for thrombus formation.²

It is by now well known that patients with arterial thromboembolic disorders have an increased risk of venous thromboembolism (VTE)—and vice versa. Hu and colleagues have here investigated which cardiovascular risk factors are associated with increased or decreased risk of VTE in general, deep vein thrombosis (DVT), and pulmonary embolism.³ They had access to genome-wide association study data linked to different risk factors from several biobanks and utilized these data for Mendelian randomization analysis. They found that body mass index (BMI) was associated with all three venous outcomes, whereas physical activity or higher systolic blood pressure might be protective, although differently for VTE in general, DVT, and pulmonary embolism.

To continue on the same theme, but in the opposite direction, Noumegni and colleagues used data from Program d'Etude des Déterminants et Interactions de la Thrombose veineuse (EDITH) cohort study on patients with VTE to identify predictors for recurrent thrombotic events on both the arterial and the venous side.⁴ They analyzed more than 30 variables, when available, from 2,011 patients. Of those, 801 had follow-up for at least 3 months after stopping anticoagulation, and the overall median follow-up was 92 months. The strongest independent predictor for VTE or arterial events during anticoagulant treatment was cancer-associated VTE, followed by unprovoked VTE.

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However, looking at VTE and arterial events separately, the predictors differed between them. For the study period after discontinuation of anticoagulation, the strongest independent predictor for VTE or arterial events was increasing age, followed by unprovoked VTE. Again, there were differences regarding individual predictors for venous versus arterial events.

Building on observation that mitochondrial dysfunction might be implicated in the pathogenesis of thrombosis, the mitochondrial gene regulators are of certain interest. The long noncoding 7S RNA has been identified as such a regulator *in vitro* as well as in cultured human cells, and therefore Wang and colleagues measured 7S RNA in plasma from 53 patients with and 184 without DVT from a previous study on diagnostic strategy.⁵ There was an independent association between 7S RNA and DVT, although not sufficiently strong to base the diagnosis of DVT on this variable.

Neutrophil extracellular traps (NETs) have also been of interest in the pathogenesis of thrombosis. Bressan and colleagues measure different serum markers of NETs in patients with acute coronary syndrome, cerebrovascular accident, or VTE as well as in patients seeking medical attention for chest pain but with no thrombosis diagnosed.⁶ Of the markers studied, myeloperoxidase–DNA complexes were significantly and independently associated with thrombotic events in general as well as with each one of them.

Clinical prediction rules are helpful for triaging patients for different levels of care. Several scoring models are used for identification of patients with pulmonary embolism at high risk of adverse outcomes. The National Early Warning Score 2 (NEWS2) is an update of the original NEWS score and includes only physiological parameters that are routinely captured in patients with suspected pulmonary embolism. Rodríguez and colleagues performed a validation study of NEWS2 for the prediction of a 30-day complicated course of pulmonary embolism, but it did not perform as well as the Bova score, which they used as a comparator.⁷

Among young adults, pulmonary embolism is more common in females than in males, due to the use of oral contraceptives, fertility treatments, and pregnancy. Bikdeli and colleagues have now investigated how elderly (≥ 65 years) females versus males differ regarding risk factors and symptoms of pulmonary embolism.⁸ They used data from the large Registro Informatizado de la Enfermedad Trombo-Embólica (RIETE) registry and the U.S. Medicare database. In both datasets, the proportion of females was higher than that of males in patients with pulmonary embolism. The authors describe here how different comorbidities and provoking factors are found more often with females or males. Regarding the symptoms, females had less often chest pain or hemoptysis but more often dyspnea compared with males. Although the differences are highly significant, the absolute differences are small and probably do not justify sex-specific diagnostic or therapeutic pathways.

Antiphospholipid syndrome (APS) is also more common in females and the risk of recurrence of thrombotic events is so high that indefinite duration of anticoagulation is commonly preferred. Although vitamin K antagonists are considered standard of care, those are often more difficult to

control in APS. Non-vitamin K antagonist oral anticoagulants (NOACs) are a much more convenient alternative but not always as effective. Marco-Rico and Marco-Vera have now reviewed the literature on trials with NOACs for VTE, arterial thrombosis, or microvascular thrombosis in patients with APS.⁹ They summarize, at the end, the current treatment recommendations and the unmet needs.

Another hypercoagulable condition is inflammatory bowel disease, with a reported risk of VTE of approximately 0.6% per year,¹⁰ and similar for Crohn's disease and ulcerative colitis. In a narrative review, Boccatonda and colleagues review the epidemiology, pathogenesis, risk factors, and treatment for VTE in these patients.¹¹ There are interesting new molecular mechanisms discovered, which may pave the way for novel therapies for inflammatory bowel disease and improved prevention of VTE.

In patients with extracorporeal membrane oxygenation (ECMO), the balance between preventing thrombosis, both in the patient and in the ECMO filter, on one hand and bleeding complications on the other hand is challenging. Due to the substantially increased use of ECMO during the recent pandemic, much information has been gathered regarding the management in adults. Intravenous heparin is the most frequently used anticoagulant for ECMO, but sometimes direct thrombin inhibitors have to be chosen, such as in case of heparin-induced thrombocytopenia. For the pediatric population, there are minimal data regarding use and dosing of direct thrombin inhibitors for ECMO, but Kiskaddon and colleagues have here performed a systematic review of the literature and they identified one prospective and 13 retrospective studies as well as several case reports.¹² Bivalirudin seems to be the most commonly reported (and probably used) direct thrombin inhibitor, but there was substantial variability in the dose regimens and the type of monitoring test used.

The final article deals appropriately with long-term consequences after DVT. There are a few scales for the severity of the post-thrombotic syndrome, but these do not take into account how the patient is functioning in daily life. Therefore, de Jong and colleagues developed the Post-VTE Functional Status scale.¹³ In this article, the authors describe how the scale was developed, its application in research, and use in clinical practice.

The 11 contributions in this latest issue of the “Recent advances in thrombosis and hemostasis” series cover a spectrum of arterial and venous thrombotic topics, with a focus on predictors and also with reviews of specific hypercoagulable conditions. There should be some articles of interest here for anyone working or interested in the field of thromboembolism.

Conflict of Interest

None declared.

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