Diagnostics in venous thromboembolism: from origin to future prospects

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Venous thromboembolism (VTE) is a prevalent and life-threatening condition that requires an accurate and timely diagnosis. The current diagnostic approach to this condition, entailing an efficient integration of clinical judgment, diagnostic imaging, and laboratory testing, is the result of decades of scientific and medical research. This article aims to present and discuss the major breakthroughs that have occurred in the diagnostic imaging of both deep vein thrombosis and pulmonary embolism, along with the various biological markers that have emerged from the laboratory bench and which have only marginally migrated to the bedside. Despite decades of research, the current diagnostic armamentarium for an efficient diagnosis of VTE remains suboptimal. Notable, a number of biomarkers has been proposed for this scope, including soluble fibrin monomers, fibrin/fibrinogen degradation products, thrombin-antithrombin complex, plasmin-antiplasmin complex, fibrinopeptide A and B, prothrombin fragments 1 + 2, thrombus precursor protein, D-dimer, activated protein C-protein C inhibitor complex, myeloperoxidase, thrombin generation assays and proteomic analysis. Several lines of evidence now attest that the global diagnostic performances of some D-dimer assays largely outperform those of any other coagulation or fibrinolytic marker proposed thus far, and a "negative" D-dimer measured with rapid enzyme linked fluorescent immunoassay or highly-sensitive immunoturbidimetric assays is now considered the biochemical gold standard for ruling out an acute episode of venous thromboembolism in a patient with a low pre-test probability for venous thromboembolism, so that additional testing can be safely omitted. However, to further improve clinical outcomes, the diagnostic efficiency of combining D-dimer testing with other markers covering different pathophysiological aspects of thrombosis such as continuous and progressive thrombin generation (e.g., activated protein C-protein C inhibitor complex, thrombin generation assays) or neutrophil activation (i.e., myeloperoxidase) merits further investigation. Proteomic analysis, which would help to characterize the structure and function of each protein and the complexities of protein-protein interactions in physiological and pathological hemostasis, also holds promise for identifying novel markers and developing effective diagnostic protocols in the future. Importantly, convincing evidence has now been provided that while D-dimer values may be effectively use for predicting the risk of recurrent thrombosis with increasing age, conventional cut-off values are inappropriate for older populations. In summary, analysis of the current scientific literature suggests that the adoption of age-dependent thresholds may increase the diagnostic effectiveness of this biomarker with increasing age. The most widely used and validated approach entails a specific formula, wherein the diagnostic threshold in patients aged 50 years or older is recalculated as follows: [age-adjusted cutoff, µg/L FEU] = [age, years]) × 10 . In a recent systematic review and meta-analysis of the scientific literature, Schouten et al concluded that age adjusted cut-off values had identical diagnostic sensitivity (i.e., 0.97) compared to the conventional D-dimer threshold, but exhibited much higher specificity across the different classes of age (i.e., 0.62 versus 0.58 in patients aged 51-60 years, 0.50 versus 0.39 in those aged 61-70, 0.44 versus 0.25 in those aged 71-80 and 0.35 versus 0.15 in those older than 80). This finding was then validated in a series of subsequent investigations.