

Pulmonary Embolism in Focus

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Venous thromboembolism (VTE), comprising deep-venous thrombosis (DVT) and pulmonary embolism (PE), is a major healthcare burden worldwide. Specifically, VTE is associated with substantial morbidity and mortality. Despite improved thromboprophylaxis, the incidence of VTE has almost been constant over the past three decades (1).

Epidemiology of PE

Until recently, detailed data of the annual number of VTE events were hard to obtain. This is due to a number of circumstances and facts: VTE is often asymptomatic ('clinically silent'), misdiagnosed, or unrecognized at death. Moreover, the decreasing number of routine postmortem examinations prevents from proper diagnosis.

Using an epidemiological model to estimate the number of community- and hospital-acquired incidents of non-fatal VTE cases and VTE-related deaths, Cohen and colleagues of the VTE Impact Assessment Group in Europe (VITAE) (2) reported in 2007 that the total number of symptomatic VTE events per annum within six EU countries was

- 465,715 cases of DVT
- 295,982 cases of PE, and
- 370,012 VTE-related deaths.

Of these deaths, 126,145 (34%) were due to sudden fatal PE, and 217,394 (59%) followed undiagnosed PE, while an estimated

27,473 (7%) only were diagnosed *ante mortem* (2).

Basically, Heit and associates from the Mayo Clinic reported similar data for the United States throughout (1, 3, 4). Accordingly, the incidence of VTE exceeds 1 per 1000; over 200,000 new cases of VTE occur in the US annually. Of these, about 30% die within 30 days; one-fifth suffer sudden death due to PE3. More recently, these numbers were reassessed.

The estimated annual incidence rates of VTE among individuals of European ancestry range from 104 to 183 per 100,000 person-years; incidence rates for PE (with or without DVT) range from 29 to 78 per 100,000 person-years; and corresponding rates for DVT alone (without PE) range from 45 to 117 per 100,000 person-years (1, 4).

Other investigators in Western Europe, North America, Australia, and Southern Latin America have shown that the annual incidence rates of VTE range between 75 and 269 cases per 100,000 persons (for review [5]). In subjects 70 years of age or older, the VTE incidence rate can increase up to 700 per 100,000 persons (5).

Diagnosis and management of acute PE

Overall, the reported numbers and estimates clearly demonstrate the extent of the above-mentioned global 'healthcare burden' and also illustrate the challenge that we are facing, in particular when managing acute PE. Consequently, the ESC Guidelines on the diagnosis and management of acute pulmonary embolism were updated in 2014 by a Task Force of the European Society of Cardiology (ESC) under the leadership of Stavros V. Konstantinides (6, 7). More recently, he and his colleagues also reviewed advances

in diagnosis, risk assessment, and treatment of acute PE and discussed current controversies (5, 8).

As outlined in the preceding editorial of this edition (9), *Hämostaseologie – Progress in Haemostasis* will reflect and reinforce some of the activities and advances in the management of PE. The current issue therefore starts with two contributions from a series of reviews written by expert investigators upon invitation by **Stavros V. Konstantinides**, who also was in charge as Section Editor, managing the peer-review of the related manuscripts. I wish to express my gratitude to Stavros for organizing the **update of PE** in the *Journal*.

Marc Righini and **Helia Robert-Ebadi** present current algorithms that have improved diagnostic accuracy and made management of PE safer (10). The authors discuss the significance of clinical pretest prediction scores, D-dimer measurements and imaging tests, specifically the importance of computed tomography pulmonary angiography. Despite the advances in diagnostic procedures of VTE, some challenges persist in certain patient populations such as pregnant women.

Patients who have survived acute PE are facing an increased risk of chronic pulmonary dysfunction and a decreased quality of life. This so-called 'post-PE syndrome' includes chronic thromboembolic pulmonary hypertension (CTEPH). **Frederikus A. Klok** and **Stefano Barco** report that CTEPH can occur in up to 12% of patients after acute PE (11). The authors review pathological mechanisms and clinical conditions that are implicated in the transition of acute PE to CTEPH. Moreover, prediction, prevention and treatment of CTEPH and other manifestations of a 'post-PE syndrome' are discussed. The series **update of PE** will be continued in an upcoming issue of the *Journal*. Comments

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on the reviews by Letters to the Editor are most welcome.

In the current edition, **Cristiana Bulato** et al. report on a boy who suffered from unprovoked DVT and PE caused by an inherited protein C (PC) defect (12). His phenotype appeared consistent with a homozygous type IIA PC defect; however, genotyping of the proband and family members revealed two distinct heterozygous gene lesions (i. e., missense mutations) corresponding to a compound PC defect. This report is a perfect example that careful characterization of the phenotype/genotype relationship will be required for proper classification of PC defects.

Zdeňka Hajšmanová et al. present a case report on their experience with idarucizumab to reverse the anticoagulant effect of dabigatran (13). The authors demonstrate that repeated administrations of the antidote are needed to overcome the direct inhibition of thrombin by dabigatran.

Misheng Zhao and co-workers identified a novel heterozygous A→C transition at nucleotide 5864 in the *FGG* gene of unrelated Chinese families, leading to a K232T substitution in the fibrinogen γ -chain (14). The investigators now report that expression of mutant γ 232T in trans-

fect CHO cells is associated with a secretion defect of variant γ 232T fibrinogen (15). This observation may explain the reported hypofibrinogenemia in affected family members.

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