

EDITORIAL COMMENT

Trends in Pulmonary Embolism Outcomes

Are We Really Making Progress?*



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Acute pulmonary embolism (PE), a potentially life-threatening manifestation of venous thromboembolism (VTE), represents a major threat to the health and occasionally the life of a large number of patients worldwide. A systematic review of the published data, performed on the occasion of World Thrombosis Day 2014, revealed an annual VTE incidence rate between 75 and 269 cases per 100,000 individuals across Western Europe, North America, Australia, and Southern Latin America (1); approximately one-third of all VTE cases present clinically as acute PE. Individuals age ≥ 70 years have a VTE incidence of ≤ 700 per 100,000 (1), indicating that an increasing number of individuals in aging societies will be at risk of developing VTE in the years to come.

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In the past decades, the favored “opening statement” of many review papers on acute PE was that “death rates remain high despite advances in diagnosis and treatment.” The study by Jiménez et al. (2) in this issue of the *Journal*, adds support to the notion that things may have begun to improve. Among 23,858 patients with acute PE enrolled in the RIETE (Registro Informatizado de la Enfermedad TromboEmbólica) registry, risk-adjusted case-fatality rates (all-cause mortality) decreased from 6.6% in the period from 2001 to 2005 to 4.9% in the period from

2010 to 2013, while PE-related death rates decreased from 3.3% to 1.8%; in parallel, there was a 32% relative reduction in the duration of hospital stay over the entire study period, from 13.6 to 9.3 days (2). These are important findings, with the strengths of the study lying on the large number of patients included, the measures taken to control and ensure the quality of data, and the completeness of the collected baseline parameters including those on patient comorbidity.

Jiménez et al. (2) are not the first to observe a favorable trend in early PE outcomes. In a population study analyzing the U.S. NIS (Nationwide Inpatient Sample), in-hospital case-fatality rates of patients with primary or secondary diagnosis of acute PE were reported to have fallen from 12.3% to 8.2% between 1998 and 2005; the length of hospital stay also decreased from 9.4 to 8.6 days during the same period (3). Another study using the NIS patient sample as well as the Multiple Cause-of-Death database reported that case-fatality rates decreased both before (from 13.2% to 12.1%) and particularly after the introduction of computed tomography (CT) angiography (from 12.1% to 7.8%) (4). Similar trends were found in the National Hospital Discharge Database covering the entire Spanish population (5). In the latter study, in-hospital case-fatality rates of PE dropped from 12.9% in 2002 to 8.3% in 2011 in parallel with a decrease in mean length of hospital stay from 12.7 to 10.0 days.

An apparent welcome explanation for the consistently favorable trends in PE outcomes shown in the present registry and in previous epidemiological studies could be that fewer patients are now dying of PE than in the past, first because diagnosis has improved—thanks to the combination of standardized clinical prediction rules, D-dimer testing, and high-accuracy multidetector CT angiography—and second because low-molecular-weight heparins have helped to optimize initial anticoagulation. However, one does not need to be an expert statistician to know

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that when a fraction such as the case-fatality rate decreases, this may be due not only to a true decrease in the numerator (the number of patients dying), but in addition, or instead, to an increase in the denominator (the overall number of patients diagnosed with PE). Indeed, the study based on the NIS reported an increase of PE cases from 126,546 to 229,637 annually during the 8-year period (3). A similar trend in crude incidence was confirmed in the Spanish population (5). It can be argued that these latter reports, along with those indicating unchanged PE-related annual mortality over time (4,6), reveal the growing problem of VTE that results from aging of the population and the proliferation of factors and situations predisposing to thrombosis. However, a trend toward overdiagnosis of PE remains another likely and equally alarming explanation (4,7). Indeed, the frequently cited study by Wiener et al. (4) found that the incidence of diagnosed PE increased by as much as 81% (from 62.1 to 112.3 cases per 100,000) following the introduction of CT angiography in comparison with the earlier reference period (1998 to 2006 vs. 1993 to 1998) (4). Increasing diagnosis of trivial, or even perhaps nonexistent, PE might artificially reduce case-fatality rates. Unfortunately, the present study by Jiménez et al. (2) could not, by design, provide further data to elucidate this critical issue, which might annihilate the perceived progress in the management of acute PE. As a further limitation of the present study, it needs to be mentioned that case-fatality rates were quite low to begin with (6.6% in the years 2001 to 2005), and this generates the suspicion the registry may have a selection bias toward a lower-risk population with PE. This is further supported by the rare use of thrombolysis (0.7% to 1.0%) or surgical embolectomy (0.3% to 0.6%) in the RIETE population (2). Early outcomes can be totally different in patients with strong evidence of right ventricular dysfunction (intermediate- to high-risk PE [8]), even if they are normotensive at presentation (9). For the present cohort, we receive only partial information on the severity of PE, as data on the patients' right ventricular status are lacking and we can only rely on the authors' calculation of the Pulmonary Embolism Severity Index, which, at least, remained stable over time (2).

Despite these concerns, there is no reason for pessimism. In fact, the present study comes "too early" for the most recent advances in our knowledge that can be expected to have a major (positive) effect on the management and, consequently, the acute prognosis of PE in the future. Among those, age-adjusted D-dimer cutoff levels (in patients age >50 years) will be helpful in optimizing the use (and preventing

the overuse) of imaging procedures, primarily CT pulmonary angiography (10). Full-dose systemic fibrinolysis is no longer recommended as primary treatment for hemodynamically stable patients with intermediate-risk PE, as its risks outweigh its benefits in this setting (11); instead, these patients should be monitored during the first days of hospital stay, and rescue reperfusion be performed (only) if hemodynamic decompensation develops despite adequate anticoagulation (8). Catheter-directed pharmacomechanical techniques are emerging as a promising option for patients with indications to reperfusion treatment and a high bleeding risk (8,12,13). Last but not least, 4 new oral anticoagulants have been approved for treatment and secondary prevention of VTE after showing noninferior efficacy and probably superior safety compared with traditional regimens of heparin followed by vitamin K antagonists (14). Importantly, the good safety profile of extended treatment with the new oral anticoagulants (15-17), but also with contemporary vitamin K antagonist-based regimens (18), may shift secondary prevention toward indefinite treatment after the first unprovoked PE episode and, thus, also decrease the disease burden related to recurrent VTE in the future.

Management of acute PE continues to evolve, with several crucial issues remaining to be resolved by future or ongoing research. These include, among others, the efficacy and safety of new oral anticoagulants in patients with cancer, the identification of candidates for early discharge and outpatient treatment, and the elaboration of follow-up strategies to determine the optimal duration of anticoagulation and identify patients at risk of developing chronic thromboembolic pulmonary hypertension. It will be necessary to face the problem of PE overdiagnosis, as well as to demonstrate the cost-effectiveness of new drugs and interventions. Decreasing the mortality attributable to acute PE will depend on the successful implementation, in clinical practice, of evidence-based, risk-adjusted diagnostic and therapeutic algorithms recommended by current guidelines. Finally, advances in management should be accompanied by campaigns to increase the awareness of the disease among health professionals and in the community, thus contributing to improved primary prevention both in the ambulatory setting and in hospitalized patients.

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