Trends in incidence versus case fatality rates of pulmonary embolism: Good news or bad news?

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The 2014 Guidelines of the European Society of Cardiology (ESC) on the diagnosis and management of acute pulmonary embolism (PE) begin with a ‘classical’ statement, which is aimed at highlighting the importance of the disease and has remained more or less unchanged for decades: acute PE may have a lethal outcome and is, in fact, a major cause of morbidity and mortality in Europe (and worldwide) (1). There is, apparently, little to oppose to this argument in light of the strong population study data from the 1980s (2), the registry data from the 1990s (3), and a frequently cited epidemiological model from the past decade (4). However, the reader who appreciates the rapidly accumulating knowledge (and evidence) on venous thromboembolism (VTE) as reviewed in the European and other international guidelines (1,5) is entitled to ask the obvious question: Have prevention improved strategies failed to result in a reduction of the incidence of PE, and have advances in management not been able to reduce death rates in the acute phase? In other words, how frequent and how lethal is acute PE at present? The strong epidemiological report by Dentali et al., which appears in the current issue of *Thrombosis and Haemostasis* and is based on hospital discharge databases from northwestern Italy covering a time period of 11 years and a population of more than 13 million, provides some valuable facts and answers, while at the same time generating further questions and new challenges (25).

Data on trends of case fatality rates can principally be derived from two types of sources: population studies analysing nationwide or regional hospital databases, and from prospective, preferably multicentre registries. The former may be criticised for being essentially retrospective and ‘uncontrolled’, notably for the suboptimal accuracy and reliability of diagnosis codes (such as the ICD-9-CM used in the present study) as entered by physicians or administrative staff during daily routine, and for the lack or incompleteness of additional indicators of comorbidity. On the other hand, and in contrast to registries, studies such the one by Dentali et al. (25) offer the advantage of very large, truly unselected populations and unbiased data. Moreover, they can provide information not only on the outcome of the individuals included, but also on annual incidence and mortality rates (and their trends) in the population, which contribute to a better interpretation of apparent changes in case fatality rates over time. For example, in a population study based the United States Nationwide Inpatient Sample, in-hospital case fatality rates of patients with primary or secondary diagnosis of acute PE fell from 12.3% to 8.2% between 1998 and 2005, and the length of hospital stay also decreased from 9.4 to 8.6 days during the same period (6). Similar trends were reported from the National Hospital Discharge Database covering the entire Spanish population (7): 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 days.

The present study which included 60,583 patients with the diagnosis of acute PE confirms and extends the existing data by showing a significant decrease of inhospital case fatality rates both in men (from 17.6% to 10.1%) and in women (from 15.6% to 10.2%) over the 11-year (2002–2012) study period (25). A further positive result, again in agreement with previous reports, is the decrease in the duration of hospitalisation for PE, although a hospital stay of 12.9 ± 9.2 days in 2012 still appears unacceptably long. Thus, taken together, the population data from three countries and two continents appear to support the conclusion that acute PE is nowadays less deadly than it used to be, and that PE-related hospitalisation costs may be declining.

This is good news, and it can be considered to reflect advances in both diagnosis (algorithms combining clinical prediction rules, D-dimer testing, and highly sensitive multidetector computed tomographic (CT) pulmonary angiography) and treatment (for the decade studied, this was mainly the establishment of low-molecular-weight heparins in initial anticoagulation) (8–10). It can also be argued that even more deaths will be prevented in the years to come by further optimising diagnostic workup with the use of age-adjusted D-dimer cut-off levels (in patients older than 50 years) to guide imaging tests (11), by safer catheter-directed pharmaco-mechanical reperfusion techniques for patients with high- or intermediate-risk and an increased bleeding risk (12,13), and, last but not least, by the increasing use of the ‘new’, non-vitamin K–dependent oral anticoagulants (NOACs). In large randomised phase 3 trials, the NOACs have demonstrated non-inferior efficacy and, at least in part, superior safety compared to traditional...
regimens of heparin followed by vitamin K antagonists (VKAs) (14–16). The NOACs may also help to further decrease PE-related costs in the future by reducing the length of hospital stay (17) or by facilitating early discharge and home treatment of PE.

The present study by Dentali et al. (25) reveals a further trend, however, which is also consistent with previous population studies (6, 7, 18): annual incidence rates of acute PE have risen significantly over time. Moreover, although the present study found that PE-related in-hospital mortality (annual deaths per 100,000 population; not to be confused with case fatality which is the proportion of hospitalised patients with PE dying in hospital) decreased between 2002 and 2012, other authors reported rather less pronounced (18) or no (19) changes in PE-related annual mortality over time. This part of the results is, or at least appears to be, the ‘bad news’. It highlights the major contribution of VTE to disease burden throughout the world (20), which continues to grow mostly due to the ageing of the population and the proliferation of factors and situations predisposing to thrombosis (reviewed in [1]). It may also indicate the persisting lack of sufficient awareness for VTE (21) and possibly the inadequacy of current prevention strategies, mainly in hospitalised patients.

Are there alternative, or additional, explanations for the opposite trends in case fatality rates versus PE incidence rates such as observed by Dentali et al. (25)? Could this constellation of findings be due to the fact that we are now more capable of diagnosing PE during life than in the past thanks to high resolution multidetector CT pulmonary angiography? The present study does confirm the significant increase in the use of CT over a time period of 11 years (25), and this trend will certainly be far more pronounced in future studies which will include more recent years. A (presumed) trend towards better diagnosis and fewer cases of failure to recognise and treat PE is likely and certainly welcome. It actually appears to be indirectly supported by the present study in which an inverse correlation between the use of CT angiography and in-hospital mortality was observed (25). On the other hand, (excessive) use of CT also comes with a downside which cannot be overemphasised, namely overdiagnosis and perhaps misdiagnosis of PE (18, 22). In this latter context, a frequently cited study 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 to the earlier reference period (1998–2006 vs 1993–1998) (18). Furthermore, a meta-analysis reported that the rate of subsegmental PE diagnosis doubled in parallel with advances in CT technology, rising from 4.7% of patients undergoing single-detector CT angiography to 9.4% of those submitted to multidetector CT (22). In that latter study, the three-month VTE recurrence risk in patients who were left untreated on the basis of a negative CT angiography remained unaffected by the use of multidetector CT (22), and it is possible that at least some of the tests were false-positive since the diagnostic specificity is low and the interobserver agreement poor at this distal level (23, 24). Increasing rates of diagnosis of trivial, or even perhaps non-existent, PE might not only mislead PE researchers to unjustified optimism by artificially reducing case fatality rates; it also represents a true risk for patients by unnecessarily exposing them to potentially dangerous anticoagulation treatment.

This study by Dentali et al. in the present issue of *Thrombosis and Haemostasis* (25) strongly supports our perception that management of acute PE is slowly but constantly improving in parallel with significant advances in diagnosis and treatment of the disease. However, it also highlights the fact that several critical issues remain to be resolved by ongoing and future research, and most of all by the translation of research into clinical practice. We are still far from observing a consistent fall in annual mortality rates (not just the case fatality rates) due to acute PE. We are even further from beginning to reverse the trend towards increasing incidence rates of PE in the population. Overdiagnosis and misdiagnosis of PE can only be reduced by ensuring the implementation by physicians (and not just the publication!) of evidence-based, risk-adjusted management algorithms as these are recommended by current guidelines (1). In addition, besides advances in treatment options, which are of course more than welcome, emphasis must be placed on targeted campaigns such as the World Thrombosis Day (www.worldthrombosisday.org), aimed at increasing the awareness of the disease among health professionals and in the community (20, 21). This is, after all, the best way to sustainably improve primary prevention of VTE and reduce the PE-related disease burden both in the ambulatory and the hospital setting.

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Conflicts of interest
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