In recent years, we have obtained new data about venous thromboembolism (VTE)—a term covering deep vein thrombosis (DVT) and pulmonary embolism (PE)—that have substantially increased interest in the problem. According to the Study on Thromboembolism in Spain,1 incidence of VTE diagnosed in-hospital is approximately 124 cases per 100 000 individuals. This represents about 55 000 new cases and 30 000 admissions per year. In direct hospital costs alone, it amounts to 60 million euros annually, of which PE accounted for 40 million euros in 2005.1

Clearly, diagnosis of VTE has improved and become more frequent. Moreover, diagnosis is often linked to healthcare, as demonstrated the 50% increase in secondary diagnosis of VTE in discharge reports over 5 years.1 The greater availability of multislice computed tomography (CT) explains the increased diagnosis of PE (up 50% in 1999-2003) but diagnosis of DVT has remained stable.1 Currently, we have access to an online registry providing updated information on the characteristics (Table) and clinical course of patients attended in daily practice in many of our hospitals (available at: http://www.riete.org).

In contrast, PE is the third cause of in-hospital death and an important cause of death in the general population. A recent European epidemiologic study2 calculated VTE causes 12% of deaths in the European population—more than diseases like AIDS, breast or prostate cancer, and traffic accidents together (543 454 and 209 926 deaths per year, respectively). In clinical practice, only 7% of deaths from PE are recognized as such because they occur during treatment for a previously-diagnosed disease. Real mortality may be up to 14 times greater.2 In many patients, PE is the direct cause of death whereas in others, it is an epiphenomenon contributing to the death of patients with substantial functional deterioration caused by other processes.3

Thus, VTE presents as a highly significant cause of mortality and morbidity and a challenge to be met in the coming years.

In the short term, prevention, risk stratification of patients diagnosed with PE, and treatment, pose considerable problems.

**Prevention**

The main argument for prevention is that in 34% of patients with PE the first manifestation is sudden death2 and 11% die in the first hour of a hemodynamic crisis. The hospital is a perfect setting to develop this disease. Pulmonary embolism is a cause of death in 5%-10% of in-hospital deaths and some 71% of deaths from PE come from VTE acquired in-hospital.2 So, the identification of at-risk patients and the application of preventative measures clearly needs improving.

**General Characteristics of Patients With Venous Thromboembolism**

<table>
<thead>
<tr>
<th></th>
<th>DVT</th>
<th>PE</th>
<th>DVT/PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>64 (17)</td>
<td>69 (16)</td>
<td>70 (16)</td>
</tr>
<tr>
<td>Men</td>
<td>52.7</td>
<td>44.2</td>
<td>49.6</td>
</tr>
<tr>
<td>Cancer</td>
<td>21</td>
<td>19.1</td>
<td>22.2</td>
</tr>
<tr>
<td>Disseminated cancer</td>
<td>9.5</td>
<td>7.6</td>
<td>10.4</td>
</tr>
<tr>
<td>Surgery</td>
<td>12.3</td>
<td>14.9</td>
<td>11.2</td>
</tr>
<tr>
<td>Orthopedic</td>
<td>3.7</td>
<td>5.3</td>
<td>4.2</td>
</tr>
<tr>
<td>Oncologic</td>
<td>1.7</td>
<td>1.8</td>
<td>1.6</td>
</tr>
<tr>
<td>Abdominal</td>
<td>1.8</td>
<td>2.4</td>
<td>1.2</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>1.1</td>
<td>1.6</td>
<td>0.9</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Vascular</td>
<td>0.6</td>
<td>1</td>
<td>0.6</td>
</tr>
<tr>
<td>Other</td>
<td>1.4</td>
<td>1.8</td>
<td>1.6</td>
</tr>
<tr>
<td>Pregnancy/post-natal</td>
<td>1.6</td>
<td>0.7</td>
<td>0.6</td>
</tr>
<tr>
<td>Thrombophilia</td>
<td>10.7</td>
<td>7.9</td>
<td>10.2</td>
</tr>
<tr>
<td>Antecedents of VTE</td>
<td>16.4</td>
<td>13.9</td>
<td>18.1</td>
</tr>
<tr>
<td>Chronic cardiac disease</td>
<td>3.8</td>
<td>8.5</td>
<td>6.9</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>8.6</td>
<td>12.9</td>
<td>12.9</td>
</tr>
<tr>
<td>&gt;4 days immobility</td>
<td>26.3</td>
<td>26.1</td>
<td>25.5</td>
</tr>
</tbody>
</table>

DVT, indicates deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.


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Thirty years ago, we knew prevention of VTE in patients undergoing major surgery avoided 8 deaths per 1000 interventions. Since then, thousands of patients are alive thanks to this discovery, the perioperative period has been converted into a setting in which preventative drugs are evaluated and surgeons currently use prophylaxis in 60% of high-risk interventions. However, we now know medical pathologies are quantitatively much more important than surgical pathologies when measuring risk of VTE. Spanish Ministry of Health and Consumer Affairs data for 1999-2003 report 35% of patients diagnosed with VTE developed the disease in hospital following admission for a medical pathology. The prognosis for these “medical” patients is worse than that of “surgical” patients; overall mortality is greater, as is death from PE and hemorrhage; incidence of severe hemorrhage is greater. The ENDORSE epidemiologic study (in press), involving many Spanish hospitals, has shown only 40% of at-risk patients admitted to hospital receive adequate prophylaxis. Clearly, we need to do better. Extrapolating from known data, in these patients, VTE prevention with heparin or pentasaccharide would lead to a highly significant reduction in the problem (RRR 44%-63%). Data from the EXCLAIM study of >4 week-long prophylaxis will soon be published. This could show additional benefits of prevention of VTE in medical patients.

Risk Stratification in Patients With Symptomatic PE

Patients with PE fall into a broad clinical spectrum ranging from those with minimal embolic load and few symptoms (50% of patients with DVT have asymptomatic PE) to those with high embolic load, presenting intense dyspnea and shock in clinical course.

Hemodynamically Unstable Patients

Patients with PE and hemodynamic instability have high early mortality. It is generally agreed they should be treated with fibrinolyis, mechanical thrombolysis, or thrombectomy. Compared with anticoagulants, fibrinolytic treatment accelerates dissolution of the clot, hemodynamic recovery, angiographic normalization, and pulmonary perfusion. The echocardiogram can show moderate or severe right ventricular (RV) dysfunction in 70% of patients (dilatation, hypokinesia, paradoxic movement of the septum, signs of low output), pulmonary hypertension, permeable foramen ovale, or floating thrombus, data that help decision-making and prognostic evaluation.

Hemodynamically Stable Patients

However, the main interest lies in detecting hemodynamically stable patients at higher risk of complications from PE. We know the most common cause of death in the first 30 days is RV failure and that RV dysfunction diagnosed by echocardiogram affects 30%-40% of hemodynamically stable patients and associates with a 2-fold increase in early mortality (30 days). In a systematic review of the first studies on this topic, the statistical association of RV dysfunction and early mortality was not particularly relevant: specificity was 55%-60% and positive predictive value (PPV), 4%-5%. However, later studies found significant association between systolic RV hypokinesia and early mortality (HR, 1.94; 95% confidence interval [CI], 1.23-3.06) that was independent of other variables of comorbidity. So, identifying these patients would facilitate selection of a subgroup that should be subject to greater clinical control.

Much more controversial is the question of whether hemodynamically stable patients with PE should receive thrombolytic treatment. The metaanalysis of published trials finds clear benefits to hemodynamically unstable patients (reduction in death in recurrent PE from 19% to 9.4%), but not the hemodynamically stable (from 4.8% to 5.3%, respectively). The first randomized, double blind study to compare fibrinolysis and anticoagulation versus anticoagulation alone in 256 patients with pulmonary hypertension or RV dysfunction showed that combined treatment improved hospital course but not early inhospital mortality (3.4% vs 2.2%). The study found no significant differences in incidence of severe or fatal hemorrhage, which was very low and might be expected to be 3-fold greater in patients treated with fibrinolytic drugs. Today, we really do need a randomized clinical trial of thrombolytic drugs versus anticoagulants in patients with PE and RV dysfunction to evaluate early mortality.

Access to echocardiography at diagnosis is limited. In Spain, <25% of patients with PE undergo echocardiography. In risk stratification, one alternative is to evaluate RV size by CT, in a 4-camera reconstruction. Right ventricular dilatation, defined as diastolic diameter RV/LV >0.9, associated significantly with greater 30-day mortality (HR, 3.36; 95% CI, 1.13-9.97), and the relation was even stronger when risk was adjusted to reduce the effect of other variables (age, pneumonia, etc) (HR, 5.17; 95% CI, 1.63-16.35). However, the specificity of CT is low (38%) as is the PPV (15.6%), so clinically it is of limited use. Notwithstanding, multislice CT has clearly displaced scintigraphy in diagnosis of PE (as well as offering higher levels of sensitivity and specificity, it may lead us to alternative diagnoses and evaluates the deep vein system) and it seems appropriate to incorporate into routine the evaluation of RV size, due to its prognostic relevancy.

The ECG plays an important role in evaluating patients because PE produces specific electrocardiographic abnormalities. When appropriately scored, these show 23.5% sensibility and 97.7% specificity for pulmonary hypertension associated with PE. However, ECG abnormalities (Daniel score >8) have proven good...
predictors of complications at 6 months in normotensive patients with PE, with 16% sensibility, 100% specificity, and 100% PPV. Moreover, in the present issue of Revista Española de Cardiología, Escobar et al report electrocardiographic abnormalities in 5% of patients diagnosed with PE associated with a 2.4-fold greater risk of death from PE at 15 days than in patients with normal ECG, indicating the former should clearly receive special attention. After analyzing the data in a logistic regression model, the authors found patients with recent-onset atrial arrhythmias represent a subgroup at special risk. Recently, a scale has been published to score electrocardiographic abnormalities in patients with PE enabling us to identify patients with echocardiographic RV dysfunction (sensibility 76%, specificity 82%, PPV 76%, NPV 86%) rather worse than that found in patients likely to develop complications inhospital (sensibility 58%, specificity 60%, PPV 16%, NPV 89%).

Biomarkers like BNP (or NT-proBNP), troponin and, to a lesser extent, dimer-D have been used to evaluate patients with PE. Initially, it was suggested they were surrogate markers of RV dysfunction and useful as a means of indicating patients for echocardiograms. Reference values vary with the technique used but the abnormalities generally correlate well with RV dilatation and myocardial damage and have an excellent NPV. So, normal BNP, NT-proBNP, or troponin values identify 90%-100% of normotense patients likely to evolve well and need less supervision during treatment. However, PPV is lower. Consequently, abnormal BNP or NT-proBNP values only identify 10%-50% of patients likely to experience complications (troponin 23%-50%) but can be used to select patients for echocardiography and greater supervision. One further advantage is that changes in values over time inform on hemodynamic evolution and its foreseeable consequences.

In normotensive patients with PE, a combination of 3 clinical data—pulse oximetry <95%, troponin elevation (>0.1 ng/mL), and electrocardiographic abnormalities—had greater sensibility (71%) and specificity (62%) to detect bad clinical course in patients with PE at 6 months (shock, intubation, recurrent PE, or death) than RV dysfunction detected in the echocardiogram (sensibility 61%, specificity 57%, PPV 36%) and improved further when BNP data were added. In view of this, it remains for us to ask whether the biologic markers together with the echocardiogram can “bring” or “add” greater precision to identifying patients with bad prognosis.

Echocardiographic RV dysfunction and troponin elevation improve the identification of patients likely to experience adverse clinical events at 3 months with greater sensibility (86%), specificity (91%), and above all, greater PPV (75%) than the echocardiogram alone. Patients with PE are at greater risk of death at 30 days (38%) if both echocardiographic RV dysfunction (RV/LV >0.9) and troponin elevation are present than patients who present with only 1 of the 2.

Whatever the case may be, we must learn more about which hemodynamically stable patients with RV dysfunction are at greater risk and can benefit from thrombolysis.

Control of Anticoagulant Treatment

Anticoagulants radically improve the natural history of VTE. Even though they increase incidence of severe hemorrhage (2.4% in the first 3 months) the balance clearly remains in their favor. Preventing complications with anticoagulant treatment does permit a small margin of improvement. Compared to vitamin K antagonists, low molecular weight heparin does not reduce incidence of severe hemorrhage in prolonged treatment although it does reduce VTE recurrence in patients with cancer. At the time of writing, new anticoagulants—dabigatran etexilate (Boehringer) and rivaroxaban (Bayer), thrombin inhibitors and factor Xa inhibitors, respectively—are undergoing clinical investigation and may represent a great advance in the management of patients with VTE and of other patients receiving them for other reasons. They are orally active and have fewer pharmacokinetic and pharmacodynamic interactions than vitamin K antagonists. They can be used from the first day and will not require periodic coagulation checks.

In patients with contraindication for anticoagulants or at high risk of PE, complications during treatment or severe hemorrhage, the use of the new temporary cava filters, which can be extracted after several weeks (overcoming the risk period), is very promising if preliminary results are confirmed.

REFERENCES


