New therapeutic options for the treatment of psoriasis create an increasing need for long-term observational studies and comparative trials in real-life situations. Well-designed cohort studies have been done on patients treated with PUVA and ciclosporin.[8,9] Similar studies are lacking for other treatment options. Smoking and increased body-mass index are associated with the onset of psoriasis,[10,11] might affect disease outcome, and therefore need to be investigated in prognostic studies. Pragmatic randomised trials are also needed to assess the value of different complex management strategies. The real challenge is to set up a truly independent research agenda that prioritises research questions and has the support to answer them.[12]

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New diagnostic strategies for pulmonary embolism

See **Articles** page 1343

Pulmonary embolism is a common, sometimes fatal, complication of deep-vein thrombosis. According to an epidemiological model, of an estimated 1 million cases of venous thromboembolism every year in six European countries, about 300 000 patients had symptomatic pulmonary embolism and about 370 000 died from complications related to venous thromboembolism.[1] Further analysis showed that 340 000 patients had sudden fatal pulmonary embolism or died from undiagnosed pulmonary embolism.

Venous thromboembolism is a typical multifactorial disease.[2] The most important risk factors are acquired and include advanced age, surgery or trauma, cancer, immobilisation, acute medical illnesses, or intake of exogenous female hormones. Over the past few years, the thrombotic risk related to long-distance travel has been better characterised. For instance, in a cohort study from the Netherlands, one of 4700 passengers on long-haul flights developed symptomatic venous thromboembolism. A third of patients had pulmonary embolism, a risk which increased with exposure to many flights within a short time-frame and with flight duration.[3] The risk of venous thromboembolism is also increased by inherited disorders, including the factor V Leiden mutation and the 20210G→A mutation in the prothrombin gene.

Venous thromboembolism is a chronic disease with a recurrence rate of about 30% after 8 years. Whether patients with symptomatic pulmonary embolism have a higher risk of recurrence than those with isolated deep-vein thrombosis is controversial. There is, however, good evidence that most patients with pulmonary embolism on presentation who have recurrence of a thrombotic event will develop symptomatic pulmonary embolism.[4,5] The case-fatality rate of recurrent pulmonary embolism is 4–9%, which should inform the counselling of patients on the duration of secondary thromboprophylaxis.

When determining the best duration of anti-coagulation treatment, the stratification of patients into groups at low and high risk for recurrence is important. In this context, routine screening for

laboratory risk factors of thrombophilia has been of limited usefulness. Recently, the stratification of patients according to risk of recurrence has been done by use of global coagulation assays, such as D-dimer or in-vitro thrombin generation assays.[6,7] To what extent this approach to risk assessment translates into improved clinical outcomes should be investigated in more detail.

Only a quarter of patients with suspected pulmonary embolism actually has the disease, and the diagnostic strategy is to attempt to rule out the disorder by combining clinical assessment, laboratory studies, and imaging techniques. In today's *Lancet*, Marc Righini and colleagues[8] report that a strategy of combining D-dimer and multislice CT is a safe and effective means of excluding pulmonary embolism. For clinical assessment, there are two reliable scoring systems.[9,10] These investigators used the revised Geneva score, a simplified version of the original score that no longer includes blood-gas analysis and chest radiography. The score is based on clinical variables that are easily identifiable: advanced age, previous venous thromboembolism, recent surgery or trauma, cancer, unilateral leg pain, haemoptysis, heart rate, and pain on leg palpation and unilateral oedema. The Wells score is also based on clinical signs and symptoms, but emphasises that alternative diagnoses are equally or more likely than is pulmonary embolism. This variable is highly operator-dependent and commonly requires extensive diagnostic procedures. Because of its high sensitivity, D-dimer testing is used in many algorithms for exclusion of venous thromboembolism. The study confirms that a negative result on quantitative D-dimer assay in patients with low or moderate pretest probability safely rules out pulmonary embolism; overall, a third of patients could be managed by clinical assessment and D-dimer testing only, without recourse to imaging techniques. In patients with a high pretest probability or positive D-dimer test, further imaging studies are needed.

In the past few years, the role of helical CT in the diagnosis of pulmonary embolism has been established. In two studies, ultrasonography of the legs was incorporated in the diagnostic algorithm.[11,12] However, the Christopher Study Investigators showed that combining pretest probability, D-dimer, and CT without ultrasonography effectively ruled out pulmonary embolism, with a 3-month incidence of venous thromboembolism of 1·3%.[13] Righini and colleagues are the first to assess this strategy in a randomised trial. They show that combining clinical assessment, D-dimer testing, and multislice CT is as safe as the approach of D-dimer testing followed by leg ultrasonography and multislice CT. Irrespective of whether ultrasonography was included, the 3-month incidence of pulmonary embolism was as low as 0·3%, with the upper limit of the 95% CI at 1·1–1·2% in patients in whom the disorder had been excluded.[8] This approach will facilitate the diagnostic work-up of patients with suspected pulmonary embolism and

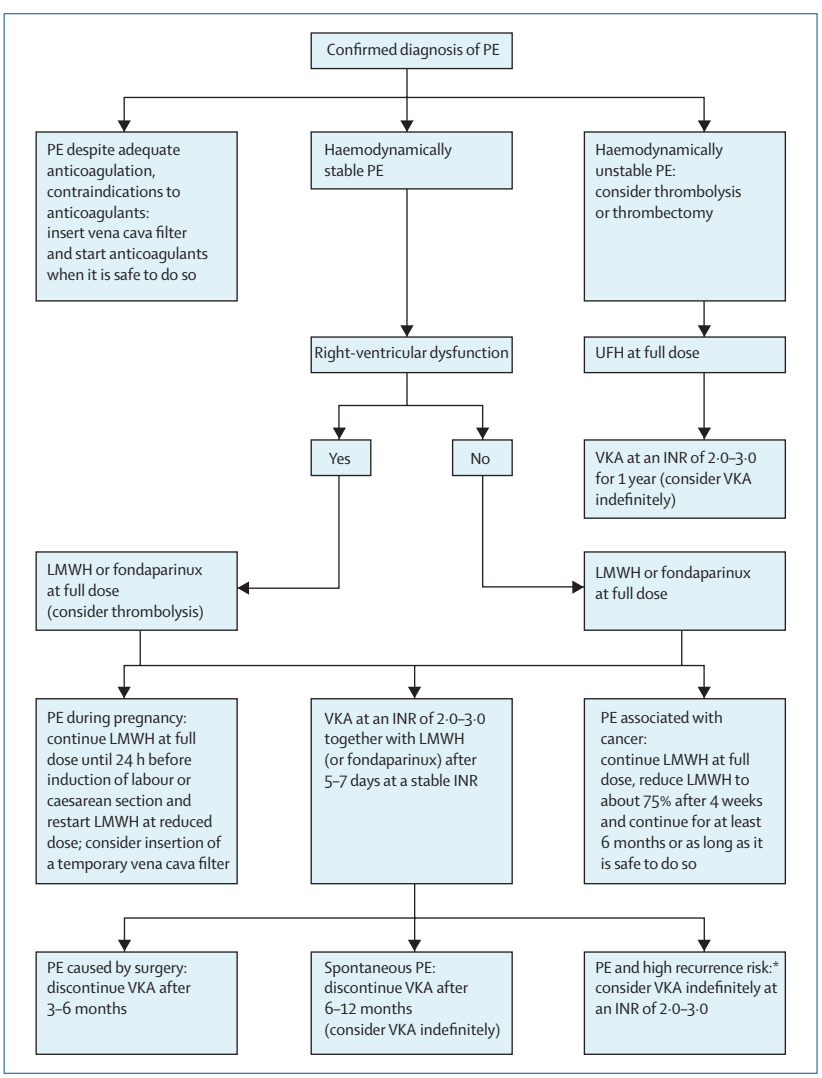

Figure: **Treatment protocol for pulmonary embolism**
PE=pulmonary embolism. LMWH=low-molecular-weight heparin. UFH=unfractionated heparin. VKA=vitamin K antagonists. INR=international normalised ratio. *Includes antithrombin deficiency, presence of the lupus anticoagulant, homozygous defects, and more than one spontaneous episode of venous thromboembolism.

seems to be cost-effective. In some patients, particularly in those with severe renal insufficiency or allergy to intravenous contrast agents, CT cannot be used. These patients, as well as those in whom a CT-based strategy is inconclusive, should have ventilation-perfusion lung scanning.

In patients with suspected pulmonary embolism, accurate diagnosis is necessary before a specific course of therapy can be started. Treatment options include embolectomy, thrombolysis, anticoagulation, or insertion of a vena cava filter (figure). In patients with massive pulmonary embolism and cardiogenic shock, thrombolysis or embolectomy should be considered. In patients with less than massive pulmonary embolism, right ventricular dysfunction visible via echocardiography or CT or indicated by high levels of troponin or brain natriuretic peptide is associated with increased risk of early recurrence and mortality.[14] Firm evidence that these patients will benefit from thrombolysis is lacking, however, and the results from an ongoing Italian study are eagerly awaited.

Placement of an inferior vena cava filter should be done in patients with contraindications to anticoagulants, severe bleeding during anticoagulant use, or recurrent pulmonary embolism while on adequate treatment. Guidelines concerning the use of vena cava filters were published in 1996.[15]

Fixed-dose, weight-adjusted, subcutaneous low-molecular-weight heparin (LMWH) is as effective and safe as intravenous unfractionated heparin.[16] LMWH is recommended by the American College of Chest Physicians over unfractionated heparin as the preferred initial course of treatment for patients with acute non-massive pulmonary embolism.[17] When given once daily, subcutaneous fondaparinux, an indirect factor Xa inhibitor, is as safe and effective as intravenous unfractionated heparin in the initial treatment of haemodynamically stable patients with pulmonary embolism.[18] Fondaparinux is approved for use in many countries, but widespread prescription is limited by its high costs. Idraparinux, a long-acting indirect factor Xa inhibitor, has been compared with a standard course of treatment consisting of heparin followed by vitamin K antagonists for several months in patients with venous thromboembolism. In the subgroup of patients with pulmonary embolism, the incidence of recurrence after 3 months in the idraparinux group was twice as high as that in patients receiving standard therapy.[19]

Several new anticoagulants, including rivaroxaban, an oral direct factor Xa inhibitor, and dabigatran, an oral direct thrombin inhibitor, are in phase III trials for treatment of acute pulmonary embolism. These new anticoagulants can be continued for secondary thromboprophylaxis after the initial treatment, a practice that is greatly superior to the current strategy of switching from heparin to vitamin K antagonists. Time will tell if these new drugs will replace current standard therapy.

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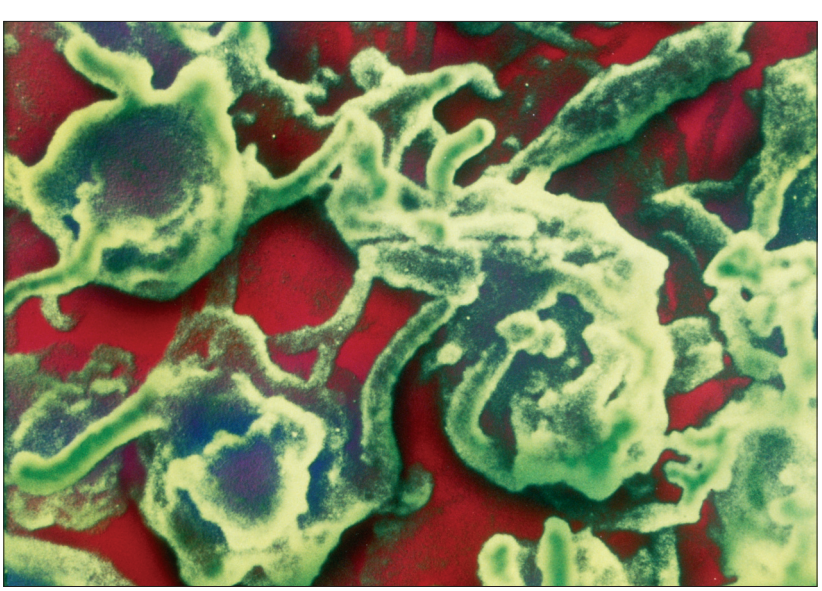
Approaching an age of reason with antiplatelet therapy

The antiplatelet drug prasugrel is one of a new generation of thienopyridines, drugs that inhibit the platelet $P2Y_{12}$ receptor. With its increased active metabolite formation, prasugrel provides more rapid and consistent platelet inhibition than does clopidogrel.[1,2] The recently published TRITON–TIMI 38 trial was the first large-scale study to assess prasugrel in patients with acute coronary syndromes undergoing percutaneous coronary intervention. The trial established that the number of ischaemic events could be reduced by increasing the potency of platelet inhibition. However, this was at the cost of an increased risk of major bleeding, especially in certain vulnerable subgroups.[3] An important and prespecified subgroup analysis of TRITON–TIMI 38, focusing on patients who received coronary stents, is reported in today's *Lancet*.[4] The so-called subgroup actually comprises 94% of the main study population, with outcomes similar to those in the main TRITON–TIMI 38 trial—an identical 0·81 hazard ratio for prasugrel versus clopidogrel for the primary ischaemic endpoint of cardiovascular death, non-fatal myocardial infarction, and stroke.

The additional valuable contribution of this current analysis is the greater insight it provides into the effects of prasugrel on stent thrombosis—a dreaded complication, and one of the biggest limitations still facing contemporary stenting. Compared with clopidogrel, more potent antiplatelet therapy resulted in lower rates of stent thrombosis in patients treated for acute coronary syndromes. Prasugrel reliably reduced the prevalence of stent thrombosis, irrespective of stent type or time period (early and late stent thrombosis) and for a broad range of clinical presentations and procedural and lesion characteristics. This effect was consistent across all definitions of stent thrombosis, including possible stent thrombosis, which likely overestimates the true incidence and potentially dilutes the reported benefit of prasugrel. Prasugrel seemed to have the greatest effect in patients at highest risk of stent thrombosis (ie, those with longer stents, bifurcation stents, impaired renal function, and diabetes). However, the authors only provided a minimum of detail on bleeding events in this analysis, and we are left uncertain as to the overall or net clinical benefit in patients in whom the risk of stent thrombosis is low or intermediate. A careful appraisal of individual clinical benefit versus the potential risk of harm is needed.

See **Articles** page 1353

The TRITON–TIMI 38 trial, one of the largest studies of percutaneous coronary intervention, found favourably low rates of stent thrombosis in patients receiving drug-eluting stents compared with bare metal stents, despite the use of drug-eluting stents in higher-risk lesions. However, we must be cautious in interpreting any perceived differences in outcomes between bare and



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Coloured scanning electron micrograph of activated platelets