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Acute and long term management of pulmonary embolism

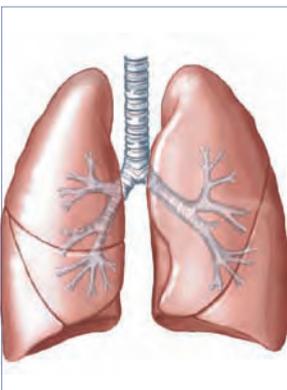
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Cardiology News



No PPI Attenuation of Clopidogrel Antiplatelet Effects: MI Registry Analysis

No significant sign of excess cardiovascular events, including death, MI, or stroke in-hospital or at one year, were seen in patients who received proton-pump inhibitors (PPIs), especially omeprazole, along with clopidogrel in a French MI registry¹.

That was seen regardless of whether patients carried a gene variant known to interfere with clopidogrel's antiplatelet action, according to investigators in a report published online January 24, 2010 in *Circulation*.

"The study reported here represents new information, not only because it uses real-life data from clinical practice but also because individual PPI treatments and the presence of CYP2C19 polymorphisms were taken into consideration, and propensity-matching was performed to compensate for confounding factors and baseline differences," according to the authors, led by Dr Tabassome Simon (Hôpital St Antoine, Paris, France).

The findings from 3670 participants in the French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI) support a large body of observational, largely retrospective data but also at least one prospective clinical trial suggesting that PPIs can be safely given with clopidogrel in patients at increased gastric bleeding risk, as covered extensively by heartwire .

But they are also at odds with other clinical evidence and ex vivo testing of platelet reactivity suggesting that PPIs may attenuate clopidogrel's protection against ischemic events. As such, they continue a long-burning controversy over whether the drugs should routinely be given to patients on clopidogrel.

"The present study provides further supportive evidence to indicate that PPIs can be used safely in patients taking clopidogrel. Although omeprazole might attenuate some of the in vitro antiplatelet effects of clopidogrel, convincing evidence is currently lacking to indicate that this combination places patients at increased risk of harm," according to Dr Michelle L O'Donoghue (Brigham and Women's Hospital, Boston, MA) in an accompanying editorial².

"Until the relationship between platelet-function assays and clinical outcomes is better delineated, the weight of the evidence suggests that clopidogrel can be administered safely in combination with a PPI for patients at risk of gastrointestinal complications," she writes.

"A growing number of large-scale analyses have now shown that the interaction between PPIs and clopidogrel does not appear to be clinically meaningful." Post hoc analyses of the huge, prospective randomized TRITON-TIMI 38 and PLATO trials found no effect from PPI use on clinical outcomes in patients receiving clopidogrel, observed O'Donoghue, an investigator with the TIMI group. But, she notes, "The most compelling evidence remains the randomized COGENT trial, which demonstrated that the combination of clopidogrel and omeprazole reduces gastrointestinal complications and does not carry excess CV risk."

COGENT, "although reassuring, is certainly not definitive. It wasn't completed, so it's not the final word," according to Dr Paul Gurbel (Sinai Center for Thrombosis Research, Baltimore, MD), a platelet expert who isn't with the FAST-MI group. Until an adequately powered prospective randomized trial is completed and provides an answer, whether there is a clinically important



PPI-clopidogrel interaction remains an open question, he told.

"Now, we have another post hoc analysis. It's more evidence there may not be an interaction. It adds another level of reassurance, but you can look at the literature and registry data and see lots of concerning data."

Gurbel pointed to the FAST-MI findings of no significant clinical effect of adding PPIs to clopidogrel regardless of patients' CYP2C19 status that is, whether they carried one or two clopidogrel "loss-of-function" alleles.

Among the two-thirds of clopidogrel-naive FAST-MI patients who received clopidogrel and contributed DNA, the odds ratio (OR) for major in-hospital events for PPI vs no PPI therapy were 0.29 (95% CI 0.06-1.44) for patients with one variant CYP2C19 allele and 1.70 (95% CI 0.10-30.3) for patients with two variant alleles in propensity-adjusted analyses. The OR was 0.70 (95% CI 0.35-1.40) in such patients with wild-type CYP2C19 alleles.

"My concern is that event rates are going in the wrong direction with respect to carrier state of CYP2C19 loss-of-function alleles," Gurbel said. The ORs point to increased risk with two variant alleles but reduced risk with one such allele, and the latter indicated lower risk than in patients without the variant. "What's up with that? It's hard to know what to do with the study."

In the propensity-matched cohort analysis of patients discharged on clopidogrel, PPI therapy was seen to pose no significant increased clinical risk. The hazard ratio (HR) for one-year stroke, MI, or death was 1.24 (95% CI 0.87-1.78, $p=0.24$) and for one-year mortality was 1.15 (95% CI 0.73-1.83, $p=0.54$).

Given that "well-conducted pharmacodynamic studies" suggest that some PPIs can attenuate clopidogrel's antiplatelet effects, O'Donoghue noted, "why does this not appear to translate into a higher risk of CV events? It is plausible that the pharmacodynamic interaction between clopidogrel and PPIs is too weak to translate into CV harm." Or, "it is plausible that platelet reactivity needs to be pushed above a certain threshold before patients are placed at increased risk," she said.

"Until the relationship between platelet reactivity and CV events is better understood, caution should be used when clinical decisions are being based on a surrogate end points rather than clinical outcomes."

On the other hand, "I believe the pharmacodynamics always correlate with clinical events," Gurbel said. "There's a tremendous body of data in thousands of patients who have had platelet-function testing after PCI that show that

people who have platelet reactivity above a certain level on clopidogrel have the bulk of ischemic events after PCI. It's pretty strong data. If you have higher platelet reactivity measured ex vivo, in vivo you probably have higher platelet reactivity, and that drives ischemic events."

There would not be an answer without the completion of a prospective, randomized trial, according to Gurbel, "but I don't know how many doctors are going to randomize their patients into a PPI/no-PPI trial, no matter what some thought leaders say, given all the overwhelming body of pharmacodynamic data showing a clear-cut interaction between clopidogrel and PPIs by ex vivo measurements." There's a lot of concern about mixing PPIs with clopidogrel among physicians in clinical practice: "I get calls about this regularly, weekly, from various doctors asking me what to do," he said.

"I'm very cautious about giving PPIs to patients on clopidogrel. I don't give them in a blanket fashion, as was common a few years ago I think it was in the discharge orders I don't think people are doing that anymore. And I would say it's not appropriate to do that anymore, based on the overwhelming pharmacodynamic data."

A recent joint consensus statement from the American College of Cardiology, the American Heart Association, and the American College of Gastroenterology, as reported by heartwire, states, "The risk reduction with PPIs is substantial in patients with risk factors for GI bleeding and may outweigh any potential reduction in the cardiovascular efficacy of antiplatelet treatment because of a drug-drug interaction³."

References:

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2. O'Donoghue ML. CYP2C19 genotype and proton-pump inhibitors in clopidogrel-treated patients: Does it take two to tango? *Circulation* 2011; DOI: 10.1161/CIRCULATIONAHA.110.006866. Available at: <http://circ.ahajournals.org>. Abstract
3. ACCF/ACG/AHA 2010 expert consensus document on the concomitant use of proton pump inhibitors and thienopyridines: A focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use. *J Am Coll Cardiol* 2010; 56:2051-2066. 21126648 *Circulation* 2010; 122:2619-2633. 21060077 *Am J Gastroenterol* 2010; 105:2533-2549. Abstract



Acute and long term management of pulmonary embolism

Pulmonary embolism (PE) is a common problem, though its exact incidence is difficult to assess due to its non-specific clinical presentation and frequently suboptimal diagnostic management affecting the quality of reporting. Dyspnoea, tachypnoea and chest pain (pleuritic or retrosternal) are the most common symptoms and signs in confirmed PE, but they are just as frequent in patients in whom this diagnosis was suspected but was ultimately ruled out. The same is true for tachycardia, syncope, cough, haemoptysis or low grade fever. While most PE episodes occur in the presence of predisposing factors and originate from venous thrombi developing in the lower limbs, deep vein thrombosis is often asymptomatic, and in about 20% of PE cases no provoking factor can be identified. Therefore a validated diagnostic strategy aimed at confirming or excluding PE should be implemented in every patient presenting with acute or recurrent cardiorespiratory symptoms and/or signs which cannot be unequivocally explained otherwise.

Mortality of a PE episode is highly related to its haemodynamic consequences. In the minority of cases - those which present with acute right ventricle (RV) failure leading to systemic hypotension the in-hospital death rate exceeds 15% despite appropriate treatment, and may be as high as >50% in patients with shock. However, in the majority of patients with PE survival can be excellent, provided adequate anticoagulation is promptly instituted. Even in mildly symptomatic patients, early diagnosis and treatment of PE is essential to prevent imminent recurrent embolic events, which may be life threatening.

INITIAL MANAGEMENT OF SUSPECTED ACUTE PE

Management of a patient presenting with symptoms and/or signs compatible with suspicion of acute PE consists of concomitant clinical assessment of the probability of the condition (pre-test probability) and of risk of early death due to PE, if indeed present. These simple assessments, based entirely on clinical history and physical examination, are required to enable the selection of an appropriate diagnostic strategy and optimal management (fig:1). Clearly, ECG, blood gases, chest x-ray and routine blood tests are most helpful in the initial differential diagnosis, including acute coronary syndromes, pneumothorax or internal bleeding. Significant hypotension and particularly shock are ominous prognostic signs regardless of their cause. In the case of a suspected acute PE, those signs indicate the 'high risk' group with expected PE related inhospital mortality of >15% despite treatment. The diagnostic approach to those patients should be maximally simplified, preferably based on urgent computed tomography (CT) angiography.

Patients not in shock and with normal systemic blood

pressure are considered 'non-high risk' for early PE related death. Further diagnostic steps should be selected after assessing their pre-test clinical probability, as it may influence both the negative and positive predictive value of some of the laboratory diagnostic tests.

Assessment of pulmonary arteries with contrast multidetector CT (MDCT angiography) is currently the core of most diagnostic algorithms. However, whenever possible or necessary, CT should be substituted by diagnostic tests which are cheaper, safer or more easily available (eg, at the bedside). Bedside echocardiography is an alternative to CT for haemodynamically unstable 'high risk' patients who are not suitable for transport. Lung scintigraphy is useful in patients with contraindications to contrast media (such as renal failure and thyrotoxicosis) or with relative contraindications to irradiation, such as pregnancy. Assessment of pulmonary arteries with magnetic resonance imaging may be also considered in such circumstances. In some clinical situations normal D-dimer values may suffice to justify withholding treatment, while positive venous compression ultrasound alone justifies anticoagulation.

The terms 'high/non-high/intermediate/low risk', which refer to PE related risk of early death, should not be confused with the different levels of 'probability' of PE (colloquially sometimes also referred to as 'risk') - for example, due to the presence of predisposing factors or suggestive clinical presentation. Because management strategies for 'high risk' and 'non-high risk' PE are different, the initial clinical staging is particularly important. Potential problems may be due to a diagnosis of hypotension, defined as systolic blood pressure either <90 mmHg or reduced by ≥ 40 mmHg compared to usual values. The latter might be difficult to establish for individual patients in an emergency setting.

For the patient with suspected 'high risk' PE, presenting with shock or hypotension, the suggested diagnostic algorithm is based on expert consensus. Diagnostic recommendations in suspected 'non-high risk' PE, taking into account the level of clinical (pre-test) probability of PE,

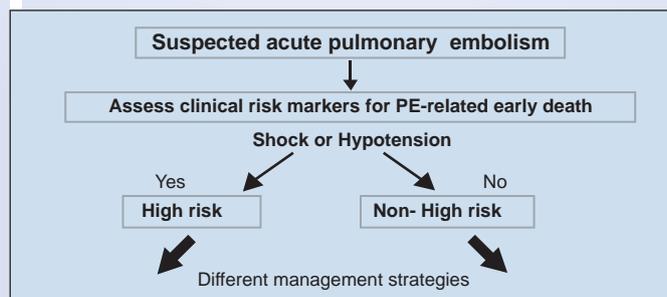


Figure 1 Initial assessment useful for selecting a management strategy in suspected acute pulmonary embolism (PE).



have been validated by outcome trials. The Polish ZATPOL registry, which assessed diagnostic strategies in 2015 patients suspected of acute PE reported from 80 hospitals, showed that using nonvalidated diagnostic criteria resulted in doubling the 30 day all cause mortality (M Kurzyna, 2010, unpublished data).

PATIENTS WITH SUSPECTED ACUTE PE AT HIGH RISK OF EARLY DEATH

Patients with suspected 'high risk' PE - that is, presenting with shock or systemic hypotension should be immediately referred for CT angiography. The absence of multiple, large, usually bilateral clots at CT angiography makes PE highly unlikely as a cause of haemodynamic instability, particularly in the absence of an increased ratio of right to left ventricular dimensions. In some of those cases CT may suggest an alternative diagnosis, such as pericardial tamponade, aortic dissection, tension pneumothorax or pneumonia.

If CT angiography is not immediately feasible the patient should be assessed using bedside echocardiography for signs of RV pressure overload and failure, which strongly support a diagnosis of PE. Their absence makes diagnosis of PE as a cause of shock/hypotension highly unlikely and should prompt further diagnostic work-up. Echocardiography is also at least as useful as CT angiography for the differential diagnosis of alternative causes of haemodynamic instability. Additional important information may include severe left ventricular dysfunction or collapsed inferior vena cava, suggesting hypovolaemia. Unfortunately RV pressure overload is not specific for acute PE. Bedside compression venous ultrasound or transoesophageal echocardiographic assessment of proximal pulmonary arteries for the presence of thrombi may help in decision making. This is particularly useful if the clinical presentation is not highly suggestive of acute PE or there are important contraindications to thrombolysis. CT angiography should always be reconsidered if the patient has been stabilised in the meantime.

A management algorithm and main recommendations which might be helpful for treating cases with suspected and eventually confirmed 'high risk' PE are suggested in figure 2 and table 1.

As soon as blood samples are drawn for haemoglobin, platelets and coagulation status, and if bleeding seems unlikely as a cause of haemodynamic instability, intravenous unfractionated heparin (UFH) should be considered and eventually started as a weight adjusted bolus (80 U/kg) followed by weight adjusted (18 U/kg/h) and later activated partial thromboplastin time (APTT) adjusted infusion. One of the potential concerns in this phase of management is a possibility of aortic dissection, with impending cardiac tamponade. Therefore, even a short echocardiographic

glimpse of the heart and ascending aorta would be most useful if the CT findings are not yet available.

While specific emergency diagnostic tests are being performed, all efforts should be undertaken to stabilise the patient. Low aortic pressure may be particularly deleterious as it further reduces RV coronary perfusion, already impaired by increased RV systolic intramural pressure. In the presence of congested jugular veins and a dilated inferior vena cava at echocardiography, any rapid intravenous fluid infusions are contraindicated. Instead, catecholamines, including norepinephrine, should be used to keep systolic blood pressure above 90 mmHg, providing a bridge for the patient to specific therapy. Oxygen supply is usually necessary. Mechanical ventilation is rarely needed and should be introduced with the understanding of its potential adverse effect on systemic venous return; therefore positive end-expiratory pressure (PEEP) should be avoided.

Preparations for definitive treatment should still be made while awaiting the results of the diagnostic tests. Potential contraindications to thrombolysis should be analysed. They will be particularly important for treatment selection in patients in whom CT was not possible and in those presenting with hypotension, but not with shock. In patients with confirmed PE and in shock the mortality risk is about 50%, with 80% of deaths occurring within 2.5 h of admission. Therefore, except in the case of an ongoing major bleeding episode or recent intracranial haemorrhage, all contraindications to emergency thrombolysis in this subgroup are considered relative. If immediate surgical embolectomy is a feasible alternative option, the risk of additional delay related to 'time to cardiopulmonary bypass' should be weighted against bleeding risk due to thrombolysis. If thrombolysis is selected as an initial treatment, cardiac surgery should be on standby as a potential second line treatment option in case of treatment failure. Repeated thrombolytic attempts are less successful than rescue surgical pulmonary embolectomy.

Short lasting high dose infusions of thrombolytics (usually

Diagnostic management of acute pulmonary embolism: key points

- Strategy should depend on initial clinical assessment of severity of suspected PE episode.
- Severity of PE should be understood in terms of risk of early PE related death rather than of clot size/position.
- In suspected high risk PE (with shock or hypotension), a simplified diagnostic algorithm based on urgent CT and/or bedside echocardiography is acceptable.
- Clinical (pre-test) probability assessment is required to interpret the results of diagnostic tests in normotensive patients with suspected PE.
- The decision not to anticoagulate (despite suspicion of PE) can be justified by the low probability of a venous thromboembolic episode in the next 3 months as indicated by an adequately validated diagnostic algorithm.
- Use of non-validated diagnostic strategies lead to worse outcome.



of 2 h) are preferred over prolonged 12 h regimens. A bolus of 0.6 mg/kg (but ≤ 50 mg) of recombinant tissue plasminogen activator (rt-PA) over 15 min is the shortest approved regimen, and is particularly useful during resuscitation. Of note, thrombolysis is a valid option also in 'high risk' PE in pregnancy. Existing evidence collected mostly from streptokinase treated patients suggests an acceptably low risk of fetal complications, mainly due to placental bleeding.

Routine filter insertion is not required before either thrombolytic or surgical treatment. Percutaneous embolectomy/thrombus fragmentation with/without local thrombolysis is still an experimental intervention. Theoretically, percutaneous interventions could be particularly helpful if acute 'high risk' PE is found during an attempted percutaneous coronary intervention in a patient initially misdiagnosed as having an acute coronary syndrome. Usually, in such circumstances, rather than moving the patient out of the catheterisation laboratory to perform CT angiography, classical pulmonary angiography is undertaken for diagnostic purposes. This makes proximal pulmonary arterial thrombi immediately accessible for catheter fragmentation or aspiration. This could be a potentially interesting therapeutic option in patients with cannulated femoral arteries who are not the best candidates for thrombolytic treatment. However, no published data exist to allow any formal recommendations.

PATIENTS WITH SUSPECTED ACUTE PE, NOT AT HIGH RISK OF EARLY DEATH

In general the management of a patient with suspected 'non-high risk' PE- that is, without shock and hypotension is compatible with a concept of 'guilty unless proved otherwise'. The first diagnostic step is the assessment of the clinical probability of PE. Reliability of its evaluation is similar regardless of whether it is assessed implicitly or based on a score assigned to preselected predisposing factors, symptoms and signs suggesting PE. Two such prediction rules - Geneva and Wells - have been prospectively validated and are recommended by current guidelines.

Because of the high risk of subsequent embolic events, heparin treatment should be started immediately in patients with intermediate and high clinical probability who do not have significantly increased bleeding risk while the definitive results of the diagnostic tests are still awaited. Pre-test clinical probability also determines the role of D-dimer and modifies the positive and particularly negative diagnostic value of the ventilation/perfusion scan (V/Q), single detector CT, and even multidetector CT angiography.

Formal confirmation of PE or deep vein thrombosis (DVT) interrupts the diagnostic process and implies prolonged anticoagulation. On the other hand a patient with

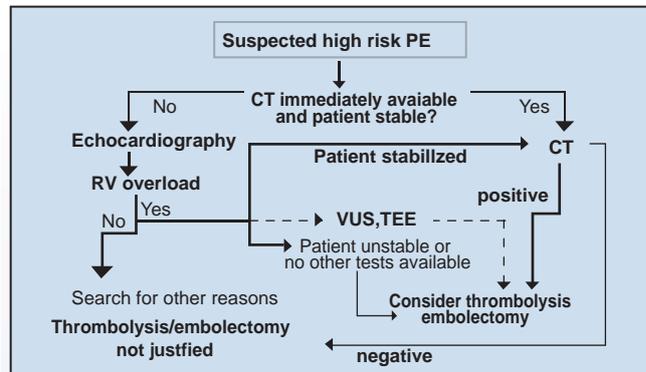


Figure 2 Diagnostic algorithm useful for patients with suspected 'high risk' PE-that is, presenting with shock or hypotension. Computed tomography (CT) angiography is a first choice test provided it is immediately feasible. Otherwise a search for signs of right ventricular (RV) pressure overload with bedside echocardiography should be undertaken. Bedside compression venous ultrasound (VUS) or transoesophageal echocardiographic (TEE) evidence of, respectively, proximal venous or pulmonary artery thrombi may greatly help in the decision to start aggressive treatment (thrombolysis or embolectomy), which is otherwise difficult to make based on indirect echocardiographic signs alone.

suspected PE should always receive specific treatment for PE until the diagnostic tests justify withholding treatment. Such justification is considered sufficient if the expected risk of recurrent venous thromboembolic episodes (VTE) without anticoagulation is $\leq 3\%$ at 3 months - similar to the risk following negative traditional contrast pulmonary angiography. A number of tests or their combinations may provide such justification.

A management algorithm which might be helpful for cases of suspected 'non-high risk' PE is suggested in figure 3.

Some confusion has been introduced by recent modification of the Wells score. Instead of three levels of pre-test clinical probability ('low/intermediate/high'), a binomial scale ('unlikely-likely') has been suggested. In addition, equal rank was recently assigned to all prediction score elements, apparently without significantly affecting its performance. Most probably it is not the choice of a particular method but the consistency of its use that is of importance. Recent guidelines for the European Society of Cardiology accept existing evidence as sufficient to consider 'low' and 'intermediate' pre-test probability in the Geneva three-level score of similar consequence for diagnostic pathways to the 'unlikely' pre-test probability in the two-level Wells score, as far as CT angiography is concerned. In contrast, a moderately sensitive D-dimer test is acceptable as a ruleout test in PE only in patients with 'low' pre-test probability of PE, while high sensitive tests are required both in the case of 'intermediate' probability and when PE is considered 'unlikely' by the two-level Wells prediction score.

Once PE is confirmed, comprehensive prognostic staging is helpful for optimising clinical management. Sub-stratification of patients at 'non-high risk' of early PE related death into intermediate and low risk groups is based on risk markers related to the severity of RV involvement due to PE. Risk markers related to RV involvement consist of signs of myocardial necrosis and RV dysfunction. Troponin



Table 1 Main recommendations for initial treatment of pulmonary embolism (PE)

In patients with confirmed high risk PE (ie, with shock or hypotension)	
ICCU admission	Is recommended
Bolus and weight adjusted intravenous UFH infusion	Is recommended
Vasopressive drugs to correct hypotension	Is recommended
Oxygen to correct hypoxaemia	Is recommended
Thrombolytic treatment	Is recommended
Surgical embolectomy	Is recommended*
Catheter embolectomy/fragmentation	May be considered*
In patients with confirmed intermediate risk PE (ie, normotensive but with RV dysfunction and/or myocardial injury)	
Weight adjusted subcutaneous LMWH or fondaparinux	Are recommended
Intravenous UFH infusion if high bleeding risk/low GFR	Is recommended
Admission to ICCU and thrombolytic treatment	May be considered
In patients with confirmed low risk PE (ie, normotensive with neither RV dysfunction nor myocardial injury)	
Weight adjusted subcutaneous LMWH or fondaparinux	Are recommended
Intravenous UFH infusion if high bleeding risk/low GFR	Is recommended
Home treatment after excluding comorbidities	May be considered
In patients with confirmed PE and haemorrhagic complications or PE recurrence despite treatment	
Permanent or retrievable vena cava filter	Should be considered
*If thrombolysis fails or is contraindicated. GFR, glomerular filtration rate; ICCU, intensive cardiac care unit; LMWH, low molecular weight heparins; RV, right ventricle; UFH, unfractionated heparin.	

elevation- assumed to result from RV injury- has been reported as being related to increased risk of adverse outcome in acute PE. Right ventricular dysfunction found at echocardiography, CT angiography, B-type natriuretic peptide/N terminal-proBNP (BNP/NT-proBNP) assessment or at right heart catheterisation was related to complicated clinical course and increased mortality. Unfortunately, for each individual marker the positive predictive value for mortality is low and the optimal cut-off point not well established. A possible additive value of the concomitant presence of signs of myocardial injury and dysfunction is likely, but not fully documented. In any case, a patient with at least one risk factor should be considered as being at 'intermediate risk' of early death (3-15% in hospital or 30 days mortality). Since approximately 25% of intermediate risk patients will have a complicated clinical course, they should be considered for close monitoring either by telemetry or in the intensive care unit, to allow early 'rescue' therapy. Patients without any of the above mentioned risk factors ('low risk' group) may be considered for early discharge on anticoagulant treatment, provided the spectrum of non-specific, prognostic markers related to general characteristics and comorbidities of the patient is reassuring.

The therapeutic approach to patients with 'non-high risk' PE- that is, without shock or hypotension- has changed little over the last decade (table 1). There is a long lasting debate over whether some of these patients should be considered for thrombolytic treatment.

Weight adjusted low molecular weight heparins (LMWH) are the first choice treatment for the majority of patients with documented acute PE, including those presenting with pulmonary infarction and haemoptysis, which usually resolves over the next few days. Fondaparinux in three fixed doses depending on the body weight (5 mg for

patients weighing <50 kg, 7.5 mg for patients weighing 50-100 kg, and 10 mg for patients weighing >100 kg) is a valid alternative, particularly in patients with renal insufficiency as it allows non-modified administration down to a glomerular filtration rate (GFR) of 20 ml/kg/min, compared to 30 ml/kg/min for the LMWH. Fondaparinux has a good publication record as far as heparin induced thrombocytopenia is considered, with only a single controversial report linking it to this potentially life threatening complication of heparin treatment. In contrast to LMWH, fondaparinux should not be used in pregnancy due to lack of evidence. LMWH usually do not require monitoring. Exceptions include extremes of body weight, particularly moribund obesity, and the pre-delivery period in pregnancy, when anti-Xa activity assessment may be considered, with uncertain clinical significance. While tinzaparin, enoxaparin, and for cancer patients-dalteparin have formal labelling for PE, it

is common practice to extrapolate existing evidence to other LMWH, with documented efficacy in DVT.

UFH started as a weight adjusted intravenous bolus (80 U/kg) followed by 18 U/kg/h and a further APTT adjusted infusion is preferred to LMWH in several clinical circumstances, including unstable and 'high risk' PE, significant bleeding risk, and severe renal failure. Starting with an adequately high dose of UFH is a main prerequisite of success. Otherwise, risk of recurrence is significantly increased. Apart from severe antithrombin deficiency, an intravenous daily dose of 30000 U guarantees effective anticoagulation even in cases without adequate APTT prolongation (defined as >1.5-2.5 control value). Slight overdosing of heparin is probably less harmful than underdosing, particularly in the first 24-48 h of treatment.

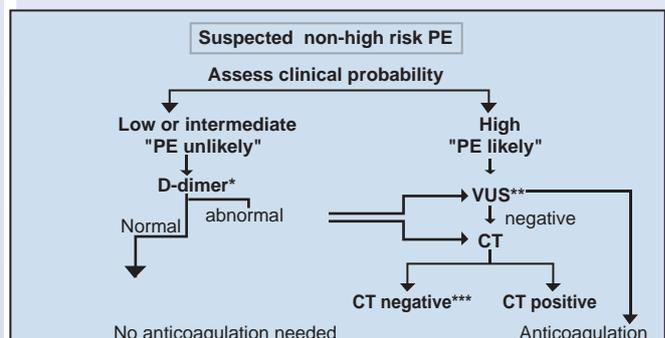


Figure 3 Diagnostic algorithm useful for patients with suspected 'non-high risk' pulmonary embolism (PE) that is, presenting without shock or hypotension. Negative D-dimer results obtained with a high sensitivity test justify withholding treatment despite low or intermediate clinical probability (*intermediate sensitivity tests can still be useful for this purpose but only in low probability patients or those 'unlikely' to have PE according to the recently introduced binominal probability scale). Otherwise, computed tomography (CT) angiography is recommended. **While positive compression venous ultrasound (VUS) may obviate the need for CT angiography, its diagnostic yield in the absence of clinical symptoms/signs of DVT is relatively low. ***VUS, ventilation/perfusion scan (V/Q) or pulmonary angiography should be considered to assist in decision making whenever a negative CT result is reported, despite a high clinical probability of acute PE.



Long term management: key points

- Prolonged secondary prevention, usually with vitamin K antagonists, is mandatory and highly effective in eliminating PE recurrence.
- The duration of secondary prevention depends on the estimated risk of recurrence.
- Previous venous thromboembolic episodes (VTE), presence of provoking factors, thrombophilia and cancer as well as bleeding risk are the most important factors to be considered and reconsidered while making decisions to continue or stop secondary prevention. Major bleeding is related to high mortality in patients anticoagulated due to venous thromboembolism.
- Venous filters should be considered in case of bleeding complications following anticoagulation after VTE.

Switching from intravenous to LMWH is often done but is not advisable, as it may be linked to increased bleeding risk.

Initial treatment with heparins or fondaparinux should be replaced by a vitamin K antagonist (VKA). Newer trends in the treatment of VTE call for starting VKA on the first day of therapy and continuing in parallel with parenteral anticoagulant in therapeutic doses for at least 4 days. The latter can be stopped only after bringing the international normalised ratio (INR) to the target range that is, 2.0-3.0 for ≥ 2 consecutive days. However, in acute PE we usually aim at 7-10 days of parenteral anticoagulation, and therefore tend to delay the start of VKA to the third day of initial treatment. In selected patients in whom optimal INR monitoring seems difficult, LMWH may be used for secondary prevention at doses recommended by the manufacturer for such purpose.

Thrombophilia does not require modification of initial treatment, with the exception of significant antithrombin (AT) deficiency. It may result in resistance to UFH manifesting as lack of APTT prolongation. Lack of APTT increase due to AT deficiency can be corrected either by increasing the dose of UFH or- in exceptional cases- by substitution of AT. The effect on LMWH efficacy is less clear, but should be suspected. It is our practice to assess AT antigen and its activity in young patients with VTE, if LMWH is selected for initial treatment.

SECONDARY PREVENTION AND MANAGEMENT OF LONG TERM CONSEQUENCES OF PE

Much has been written on the strategy of secondary prevention of VTE. Clearly it should depend on the underlying causes of the thromboembolic event. In patients with a strong and obvious predisposing factor, which could be removed, 3 months of anticoagulation is considered sufficient. Nevertheless, a 3% annual risk of VTE recurrence can still be expected. The decision regarding the duration of secondary prevention, in the case of permanent predisposing factors or 'idiopathic' unprovoked PE, is more difficult. The annual incidence of VTE may exceed 10% and does not seem to decrease notably with

time elapsed since the index event. Clear recommendations can be made for patients at highest risk: those with a history of previous VTE events, antiphospholipid syndrome or untreatable malignancy. All are candidates for chronic, life long anticoagulation. Patients with cancer require secondary prevention with LMWH instead of VKA, as it seems to improve their survival, at least when given during the first 6 months after an acute VTE event. An abnormal level of D-dimer assessed 1 month after stopping VKA was highly predictive of a high recurrence rate, which can be successfully abolished by continued treatment. Unfortunately, a negative result of a D-dimer test 1 month after a discontinuation attempt does not guarantee safe

withholding of secondary prevention. This population of patients is in clear need of additional markers for further risk stratification for VTE recurrence.

An individual's risk of bleeding may also decide about continuing or stopping secondary prevention. In fact, chronic anticoagulation is highly efficient in preventing recurrent VTE events, but at a cost of a major bleeding rate of 3-4% within, and up to 5-9% outside, controlled clinical trials. Bleeding complications during the first 3 months of treatment are strong determinants of mortality. Even though most serious bleeding events occur in the first months of anticoagulation, periodical reassessment of indications and contraindications to continued VTE prevention, accounting also for the patient's preferences, is still very important. Increasing use of potent antiplatelet therapies following cardiovascular interventions represents a new challenge for prophylactic long term anticoagulation.

Most survivors do not experience any significant long term consequences of an acute PE event, except for chronic venous insufficiency related to concomitant DVT. A small, so far not precisely estimated subgroup (0.1-5%) remain with postembolic organised thrombi that may increase RV afterload. Pulmonary vascular remodelling in over perfused non-obstructed areas may result in progressive chronic thromboembolic pulmonary hypertension (CTEPH). There is no generally accepted strategy of follow-up of acute PE survivors. However, echocardiographic follow-up is certainly advisable in all survivors of acute PE who remain symptomatic or develop exercise limitation due to dyspnoea with time.

In the case of signs suggesting RV pressure overload, comprehensive pulmonary vascular imaging and eventually right heart catheterisation is recommended. Indeed, differential diagnosis may be difficult due to several common causes of chronic pulmonary hypertension. On the other hand, a diagnosis of CTEPH must be unequivocally confirmed as it should lead in most patients to pulmonary endarterectomy.

Ref: Acute and long term management of pulmonary embolism. Adam Torbicki. Heart 2010;96:1418-1424.



Insight

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Cardiology News

Everolimus-Eluting Stent Superiority Persists at Three Years

The superior safety and efficacy of everolimus-eluting stents (EES) over paclitaxel-eluting stents (PES) persists at three-year follow-up. Earlier studies comparing EES with PES showed significant decreases in in-segment late loss at eight months, noninferiority for target vessel failure at nine months, and significant decreases in target vessel failure and major adverse cardiac events (MACE) at two years with EES. Treatment with EES resulted in a significant 30% decrease in target vessel failure and a significant 43% decrease in the rate of MACE compared with PES. The differences were driven by a significant 39% decrease in ischemia-driven target lesion revascularization and a trend toward a 38% decrease in the composite endpoint of cardiac death or myocardial infarction. The two groups didn't differ in rates of stent thrombosis. When follow-up was subdivided into two periods, the rates of adverse events were nonsignificantly lower with EES than with PES from the procedure through year one and between years one and three, with the exception of target vessel failure which decreased to a similar extent with EES compared to PES in both periods. Among diabetics, however, there was no significant difference in three-year rates of MACE between EES and PES.

Am J Cardiol. Posted online January 19, 2011

Atrial Flutter Responds Well to Cardioversion in the Emergency Dept.

Atrial flutter in emergency department (ED) patients resolves more often with electrical cardioversion than with antiarrhythmic drug treatment, and long-term outcomes are good. As for measures of ED outcomes, 91.3% of patients undergoing electrocardioversion achieved normal sinus rhythm compared with 26.7% of those given antiarrhythmic medication. Furthermore, 93.5% of the electrocardioversion group versus 60.0% of the medication group was discharged directly home. Discharge rates were 93.3% among patients with spontaneous cardioversion, 58.3% in those given rate-control medication only, and 95.4% among the group not treated in the ED. The 46 patients managed with electrocardioversion were relatively young and low risk, and the majority had received successful cardioversion before. High success and low complication rates in this group suggest that electrical cardioversion may be an appropriate ED strategy for low-risk patients with atrial flutter. Conversely, oral and intravenous antiarrhythmic medications seldom achieved conversion to normal sinus rhythm.

Ann Emerg Med. Posted online January 20, 2011.

Surface ECGs May Help Predict Left Bundle Branch Block Prognosis

Standard surface electrocardiograms can help detect right ventricular (RV) dilatation in patients with heart failure and left bundle branch block (LBBB). Electrocardiographic criteria of RV dilatation were terminal positivity in lead aVR, low voltage (below 0.6 mV) in all extremity leads, and an R/S ratio below 1 in lead V5. When values of the three criteria were examined separately, none reached a high predictive value. In comparison with echocardiography, however, the team found that any combination of 2 to 3 positive criteria could predict an indicative RV base-to-apex length with a positive predictive value of 89% and a negative predictive value of 88%. For increased RV diastolic area the corresponding values were 80% and 88%.

Am J Cardiol. Posted online December 24, 2010.

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Editorial Note

Dear Doctor,

We are happy to present the 20th issue of "Insight Heart". It is a small endeavor to provide you compiled & updated information on cardiovascular diseases and its management. This issue is focused on "**Acute and long term management of pulmonary embolism**". We will appreciate your thoughtful comments.

Thanks and regards.

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