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ANMCO Position Paper: long-term follow-up of patients with pulmonary thromboembolism

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Venous thromboembolism (VTE), including pulmonary embolism and deep venous thrombosis, is the third most common cause of cardiovascular death. The management of the acute phase of VTE has already been described in several guidelines. However, the management of the follow-up (FU) of these patients has been poorly defined. This consensus document, created by the Italian cardiologists, wants to clarify this issue using the currently available evidence in VTE. Clinical and instrumental data acquired during the acute phase of the disease are the cornerstone for planning the FU. Acquired or congenital thrombophilic disorders could be identified in apparently unprovoked VTE during the FU. In other cases, an occult cancer could be discovered after a VTE. The main targets of the post-acute management are to prevent recurrence of VTE and to identify the patients who can develop a chronic thromboembolic pulmonary hypertension. Knowledge of pathophysiology and therapeutic approaches is fundamental to decide the most appropriate long-term treatment. Moreover, prognostic stratification during the FU should be constantly updated on the basis of the new evidence acquired. Currently, the cornerstone of VTE treatment is represented by both the oral and the parenteral anticoagulation. Novel oral anticoagulants should be an interesting alternative in the long-term treatment.

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Epidemiology and pathophysiology

Venous thromboembolism (VTE), including pulmonary embolism (PE) and deep venous thrombosis (DVT), is the third most common cause of cardiovascular death; particularly PE is often difficult to define because it can be present with a wide spectrum of symptoms: indeed, it may remain asymptomatic or sometimes its diagnosis may be incidental. Moreover, in over 30% of cases, sudden death may be the first presentation of PE and more than half of the deaths caused by PE, remain undiagnosed during life.

Currently, medical decision-making is increasingly supported by International Guidelines,[1] which are often periodically updated and nationwide contextualized.[2,3] However, these recommendations are in most of the cases primarily addressed to the treatment of the acute phase of the disease lacking a scientific contribution dedicated to the post-acute phase. Also the 2014 European Guidelines on PE,[1] as pointed out by Rugolotto and Favretto[4] in a recent editorial 'does not offer specific guidance on follow up and long term management of PE'.

The relevance of long-term follow-up (FU) could be deduced by a recent Danish survey, which enrolled a population of 120 000 cases of confirmed VTE between 1980 and 2011. The authors reported that these patients were at increased risk of death during the first year after diagnosis and the elevated risk persisted during the 30 years of FU. While 30 day mortality after DVT remained constant over that period, it markedly improved for PE.[5] According to the authors, individual counselling aimed at tailoring the therapy and intervening on the risk

factors reduces the recurrence of VTE, thereby preventing related deaths.

It has been reported that about half of the patients, between 6 months and 3 years, following the acute PE episode, referred subjective dyspnoea and/or reduced exercise tolerance; these symptoms have been objectively confirmed by the 6-min walk test (6MWT) and are frequently related to higher pulmonary arterial pressure (PAP) and right ventricle (RV) dysfunction.[6] Exertional dyspnoea is a frequent symptom in the long-term clinical course of acute PE. However, in several cases, this symptom is likely to be unrelated to the past thromboembolic event because these patients often suffer from several cardiopulmonary co-morbidities and risk factors, such as older age, obesity, and smoking habits, which could also be considered as independent predictors of VTE.[7]

Actually, the role of the 'diagnostic delay', which is the period between the onset of symptoms and PE diagnosis/treatment, remains unknown.[8] At discharge, the prognostic stratification performed in the acute phase should be reformulated considering both the gravity and the PE extension besides the associated co-morbidities. Furthermore, it is essential to obtain definitive information about the presence or persistence of deep vein thrombosis (DVT), haemodynamic instability, right ventricular dilatation, and inherited thrombophilia.

These data are useful to plan a 'personalized management' of the patients choosing the more appropriate treatment.[9] The aim is to avoid recurrent PE and bleeding events. Moreover, this approach allows the early recognition of pulmonary arterial hypertension (PAH) and post-thrombotic syndrome (PTS). With this background, our clinical group has decided to fill the gap regarding the management of VTE FU proposing the possible therapeutic and diagnostic approaches. Indeed, to our best knowledge, this issue has been neglected to date.

Results of records

In medical practice, the VTE FU generally ends with the discontinuation of anticoagulant therapy; however, it is known that after the acute phase, the patient's clinical course could be complicated by several and serious adverse events. Moreover, in some cases, these complications may also occur during anticoagulant treatment. Recurrent VTE, chronic thromboembolic pulmonary hypertension (CTPEH), and arterial thrombotic events are some of the possible complications, which are all related with a higher risk of death.[10,11]

To clarify the management of VTE FU, last international registry on PE and/or DVT may be useful to understand the problem, giving also some suggestions about the most appropriate clinical management.

To date, only four prospective registries have considered the FU of VTE:

- International Cooperative Pulmonary Embolism Registry (ICOPER)[12];
- Italian Pulmonary Embolism Registry (IPER),[13] which included only patients with PE;
- Registro de Informatizado Enfermedad thromboembolic (RIETE)[14]; and
- MASTER.[15]

ICOPER is an international registry that included 2454 consecutive PE patients, enrolled in 52 hospitals in 6 different countries, between January 1995 and November 1996. Inclusion criteria were:

- PE (asymptomatic or symptomatic) diagnosed within 31 days from symptoms onset and
- PE diagnosed at autopsy.

PE diagnosis was done by the physicians of the recruiter centres without an independent revaluation. At admission, 2182 patients (88.9%) were symptomatic and haemodynamically stable, 103 (4.2%) were haemodynamically unstable, and 169 (6.9%) asymptomatic. The mean age of the population was 62.3 years; 63% of the patients were older than 60 years of age.

The aim of the registry was to evaluate the 3 months mortality rate. FU was completed by 98% of patients. Three months mortality was 17.5%. Note that 45.1% of deaths were attributable to PE, 17.6% to cancer, 11.8% to sudden death, 11.8% from respiratory distress, 2.5% to a bleeding event, 2.5% to a stroke, 1.3% to acute coronary syndrome, and 7.3% to other causes. PE recurrence after 3 months was 7.9%. Mortality rates were 33.7% and 46.8% after 14 days and 3 months, respectively.

Statistical analysis revealed that age >70 years, cancer, chronic obstructive pulmonary disease, heart failure (HF), systolic blood pressure <90 mmHg, respiratory rate >20/min, and a hypokinesia of the RV at presentation were independent predictors of death.

IPER is a multicentric, web-based, prospective Italian registry including patients with confirmed PE, enrolled in 49 Italian centres (58% cardiology departments and 42% internal medicine department). The aim of the registry was to:

- describe the demographic and clinical characteristics of patients with PE;
- describe the strategies used for the diagnosis, prognosis, and therapy; and
- prospectively collect data on clinical course during both the hospital phase and the FU.

Patients were enrolled between August 2006 and August 2010. The 4-year FU ended in August 2014. In particular, the registry enrolled 1716 patients (mean age 70 ± 15 years, 43% men). In-hospital mortality rate was 6.8%. The mortality rate between discharge and 12 months FU was 12.8%. Of the 1600 patients who survived hospital admission, FU data after 12 months were obtained for 656 patients (41% of survivors, mean age of 69 ± 15 years; 42% men). Risk factors statistically associated with higher risk of death were age cancer, cancer diagnosed during hospitalization, and underweight. Mortality in patients with provoked and unprovoked PE was statistically significant (16.1% vs. 3%, $P<0.001$). In patients with provoked PE, death was generally due to

cancer, while in unprovoked PE death was due to atherosclerotic events.

In conclusion, short-term outcome was related to the haemodynamic stability at admission. Furthermore, the short- and long-term survival were related to the presence/absence of co-morbidities.

Riete is a prospective, web-based, multicentre international registry. Enrolment is still ongoing. Riete registry includes patients with VTE (DVT, PE, or DVT + PE) with the aim of recording data during both the acute phase and the FU. In particular, it has enrolled patients with symptomatic and objectively confirmed VTE. Diagnosis of DVT was performed by venography, ultrasound, or venous impedance plethysmography. PE was confirmed with pulmonary angiography, lung scan, and computed tomography (CT) angiography. The patients were treated according to the best practice of each recruiter centre. FU was planned for at least 3 months after the acute event, but no limit on the duration was recommended in the protocol. Among the 14 391 patients enrolled in 2006, 2945 (20%) had an active cancer; these patients had in the first 3 months a higher rate of fatal PE and fatal bleeding in comparison with the patients without cancer (2.6% vs. 1% and 1.4% vs. 0.3%, respectively). Chronic kidney disease, metastases, recent major bleeding, and immobilization were the independent risk factors for fatal PE or bleeding events. A lower mortality rate for obese patients was observed, although not a statistical difference in PE recurrence. Renal insufficiency was related to a higher level of fatal EP and bleeding, but according to the authors, the higher risk of PE justifies the anticoagulation therapy.

Riete registry analyse also the VTE in pregnant women. In particular, 40% of VTE occurred during the first trimester suggesting that, when indicated, prophylaxis should be initiated as soon as possible. No bleeding events were reported before childbirth; however, after that, the risk of major bleeding was greater than the risk of recurrent PE (5.6 vs. 1.4%).

The authors of the Riete registry have compared the role of Pulmonary Embolism Severity Index (PESI) with the Simplified Pulmonary Embolism Severity Index (sPESI) reporting no differences between the two scores.

MASTER is a web-based, prospective, multicentre Italian registry that included 2119 patients with confirmed VTE (1541 DVT, 206 PE, and 372 DVT + PE) with a 24 month FU. The aim of the study was to collect data on the patient's clinical management. Almost all enrolled subjects received anticoagulation for at least 6 months.

Mortality data obtained in 2021 (95.4%) patients showed a mortality rate of 4.5%: 1.43% in unprovoked VTE, 20.3% in cancer patients, and 1.7% in patients with transient risk factors. Cancer [hazard ratio (HR): 7.2], medical treatment with heparin (HR: 2.5), in-hospital treatment of VTE (HR: 2.0), ileo-caval thrombosis (HR: 1.7) were independent predictors of death. Conversely, the use of compression stockings was associated with a low risk of death (HR: 0.6). Note that there were no differences, regarding mortality in patients with PE and DVT. In the 1988 (93.8%) patients followed for recurrence, 124 (3.63%) patients had at least one recurrent VTE, 101 (81.5%) DVT, and 23 (18.5%) PE. Frequency of recurrent VTE in patients with previous unprovoked or provoked PE were 4.5% and 2.6, respectively. Rates of recurrent VTE in cancer patients was 2.6%. Patients with a first episode of DVT had a recurrent DVT in 6.0% and a PE in 0.6%. Male gender and cancer were independent predictors of recurrent VTE (HR: 1.7 and 1.6, respectively). Conversely, the presence of transient thromboembolic risk factors was associated with a lower incidence of events (HR: 0.4). Statistically significant was the mortality rates of patients with recurrent VTE compared with those without recurrence (16.5 vs. 4.2%, $P<0.001$). Data regarding bleeding events, PTS, cancer, and arterial thrombosis were obtained in 1883 patients, with bleeding occurring in 1.7% of patients treated with heparin and 2.7% using vitamin K antagonists (VKAs) [odds ratio (OR): 0.6]. The incidence of major bleeding events was 2.5%; in particular, 5.5% in patients with known or occult cancer and 1.8% in patients without cancer. The incidence of PTS was 9.7% (182 of 1883): in this case, patients with and without cancer were 25% and 5.9%, respectively. Cancer was found in 1.3% of patients during the FU, while atherothrombotic complications occurred in 1.1% (20 of 1883).

Type and timing of follow-up

Previous results and daily clinical experience suggest that the main objectives to be pursued during the VTE FU could be summarized as follows:

- assess the global cardiovascular risk;
- define the anticoagulation therapy and its duration;
- assess the risk of bleeding;
- early recognition of complications (recurrent VTE);
- identify patients with CTPEH [WHO Group 4 of pulmonary hypertension (PH)];
- evaluate the possibility of PTS of the lower limbs and/or DVT; and
- identify, as soon as possible, the presence of an unknown cancer or a prothrombotic condition.

To perform a correct FU, it is necessary to identify the useful tools and the correct timing.

Biochemical markers and thrombophilia

Biochemical markers

The duration of anticoagulation as described in following parts of this document must be planned on the basis of several factors, mainly for the risk of recurrence of VTE and the risk of bleeding.

D-dimer test assessment may be useful, because it is able to discriminate patients at low risk (<5% per year), in which the anticoagulation could be suspended. Two recent meta-analyses[16,17] have confirmed that elevated D-dimer levels after 1 month from anticoagulation withdrawal are associated with a significantly increased risk of recurrent VTE. Two scores have been proposed to assess the individual risk of VTE recurrence and both include the result of the assessment of D-dimer after 1 month of treatment discontinuation.[18-20] More recently, another study has shown that the serial D-dimer assessment, performed during the 3 months after the withdrawal of anticoagulant therapy, could be useful to identify those subjects with very low risk

of VTE recurrence. It is recommended to assess the D-dimer serially in the first 3 months after withdrawal of anticoagulation; a normal persistent result could allow to finally stop anticoagulation that on the contrary must be continued in patients with persistent elevation.

Thrombophilia

Venous thromboembolism is considered to be a consequence of the interaction between patient-related, usually permanent, risk factors and setting-related, usually temporary, risk factors. Generally, VTE is considered to be 'provoked' in the presence of a reversible risk factor (surgery, trauma, immobilization, pregnancy, oral contraceptive use, or hormone replacement therapy) within the last 6 weeks to 3 months before the acute event. The presence of persistent, as opposed to major, temporary risk factors is fundamental for the choice of the duration of anticoagulation therapy after a first episode. Moreover, the distinction based on the aetiology influences also the risk of recurrent VTE. Indeed, recurrent rate is generally lower in provoked compared with unprovoked VTE.

Congenital thrombophilic abnormalities are labelled as persistent factors. It has been estimated that thrombophilic abnormalities range from 5% to 10% in the general population. A prevalence of 40% in patients with VTE has been reported in literature. However, some thrombophilic abnormalities may be acquired during life (lupus anticoagulant and hyperhomocysteinaemia). Several evidence confirmed that thrombophilic mutations have a different clinical penetrance. In fact, a higher thrombotic risk has been reported in subjects with congenital deficit of protein C or S or in the presence of one of the following defects: homozygous mutation of the factor V Leiden, G 20210A mutation of the prothrombin, or in case of double heterozygous or multiple defects. The aforementioned mutations are quite rare. A higher prevalence has been reported for heterozygosity of factor V Leiden or prothrombin mutations. However, these subjects seems to be at lower risk.[21]

In general, the presence or absence of thrombophilia does not modify the therapeutic management during the acute phase of VTE. Currently, the influence of thrombophilia on the duration of anticoagulant treatment is still debated. At the same manner, whether it is useful or not to investigate thrombophilia in patients with VTE after the acute phase, especially for VTE recurrence, has not yet been clarified. Some authors believe that there are no significant benefits in carrying out such investigations,[22–24] while others support them, especially stressing that the increased risk of recurrent VTE could be associated with thrombophilic defects.[25,26] In general, thrombophilic screening must be recommended to those patients with a positive familiar history of VTE or recurrent disease.

The tests to be performed, are presented in *Table 1*.

The recommendation of the appropriate timing to carry out the investigation are shown in *Tables 1* and *2*.

Echocardiography

During the VTE, FU is essential to identify those patients with PAH. Transthoracic echocardiography (TTE) may detect RV pressure overload. In these cases, chronic thromboembolic pulmonary hypertension (CTEPH) must be evaluated, because this condition could be treatable with surgery. However, it should be noted that there is a lack of indication regarding:

- which patients must be submitted to echocardiographic FU;
- timing of TTE;
- which echocardiographic parameters (and respective cut-off) must be considered; and
- further diagnostic tests in case of CTEPH

With regard to the first issue, several prospective studies affirmed that is not reasonable to refer all survived PE patients indiscriminately to serial echocardiographic examinations.[27,28] According to these authors, it would be helpful to select the patients on the basis of clinical data and symptoms.

It seems reasonable that every patient with a diagnosis of PE at intermediate risk receive an echocardiographic examination. In this way, it is possible to obtain the correct prognostic assessment, especially for those patients classified as no high risk.[2]

TTE should also be performed at discharge, especially if a right ventricular dysfunction (RVD) and/or PAH have been observed during the acute phase. Moreover, in the presence of the aforementioned abnormalities at discharge, an echocardiographic FU must be considered.

Some considerations must be said about the timing for TTE during the FU. If echocardiographic abnormalities are associated with moderate exertional dyspnoea, the patient should be re-evaluated clinically and by TTE within 3 months after discharge. In the absence of symptoms, TTE may be performed between the 3rd and the 6th month (when also anticoagulant therapy could be discontinued). The persistence of echocardiographic signs suggestive of PAH after 3 months from the acute event must raise the suspicion of a chronic condition. In this case, serial TTE evaluation must be performed on the basis of clinical symptoms.[29]

Even though the gold standard for the evaluation of PAP is the right heart catheterization (RHC), an echocardiographic evaluations could give important information and remains the method most widely used.

The European Society of Cardiology, in 2015, in the 'guidelines for the diagnosis and treatment of pulmonary hypertension',[30] has suggested some echocardiographic criteria for the estimation of the PAP, based on tricuspid regurgitation velocity and the presence of other echo 'PH signs' to identify the probability of PH as low, intermediate, or high.[31]

In a 12 month echocardiographic FU, 286 patients enrolled in the Italian IPER registry[32] and evaluated with an echocardiogram within 24 h have showed that an RV–right atrium (RA) gradient >45 mmHg during the FU (PAH likely) was present only in a small percentage of cases (2% of the total), and all these patients had an RV–RA gradient >45 mmHg at baseline TTE. In this group, only 6% of patients maintained a gradient >45 mmHg during the FU. No patients without tricuspid insufficiency or an RV–AD gradient ≤45 mmHg at baseline TTE were classified as

Table 1 Thrombophilic tests

Dosing	Searching
Antithrombin	Factor V Leiden
Protein C	G20210A mutation
Protein S	Lupus anticoagulant
Homocysteinaemia	
Antiphospholipids antibodies (anti-cardiolipine and anti-beta-2 glycoprotein-1)	

Table 2 When thrombophilic tests must be performed

- Evaluation of hypercoagulable state may be performed at any time, independently from the anticoagulation treatment.
- Evaluation of protein C and S, which are vitamin K-dependent factors, should not be performed during the treatment with vitamin K antagonists.
- Evaluation of thrombophilic defects should not be performed during the treatment with the new oral anticoagulants.
- Pregnancy modifies the levels of protein C and protein S (higher and lower levels, respectively)

The tests should NOT be routinely performed:

- During the acute phase of venous thromboembolism (possible consumption of physiological anticoagulants factors)
- During anticoagulant therapy
- During pregnancy

Tests are usually performed:

- After 3 months form the acute event;
- After permanent or temporary suspension of anticoagulant treatments (after 15 days and 48 h for vitamin K antagonists and new oral anticoagulants/heparin, respectively)

Partial screening should be avoided.

probable PAH during the FU.[33] Moreover, only 8% of cases during the FU had TTE findings compatible with PAH; all these patients had been already identified at baseline. In this study, it has not been possible to obtain the confirmation of PAPs with cardiac catheterization in the majority of suspected cases. However, patients most severely compromised were stratified as PAH likely during the FU: two patients underwent pulmonary endarterectomy (PEA) and one was treated with oxygen home therapy.

Finally, there is a unanimous consensus that a perfusion lung scan should always be performed if echocardiographic assessment is suggestive of intermediate or high probability of hypertension following a PE patient.

Table 3 summarizes the recommendations for the execution of TTE.

Lung scan, computed tomography scan, and magnetic resonance

Magnetic resonance imaging (MRI) has been rarely used in the diagnosis of PE and has no use in the FU.

Computed tomography, especially for the high radiation burden, is not feasible as a routine test for the FU in VTE, despite its predominant role in the diagnosis of the acute phase.

Of greater importance in the FU of PE patients could be the lung scintigraphy (LS), because it is able to evaluate lung perfusion and indirectly the overall pulmonary embolic burden.

The LS in clinical trials was generally performed by evaluating both the lungs ventilation (V) and perfusion (Q) either by planar technique (V/Q scan) or by tomographic technique (V/Q SPECT).

V/Q SPECT seems to have a superior diagnostic performance compared with planar V/Q scintigraphy; however, no direct comparisons between the techniques have been performed during PE FU.

Meneveau *et al.*[34] demonstrated that residual pulmonary vascular obstruction (RPVO) evaluated before hospital discharge in patients with intermediate- to high-risk PE was a powerful prognostic factor for a 6 month outcome. Moreover, RPVO $\geq$35% was associated with an increased risk of adverse events at 6 months. In fact, at 6 months, 32 patients (7.7%) had at least one adverse event: 12 deaths (2.9%), 12 recurrent PE (2.9%), and 14 (3.4%) HF. Independent predictors of combined endpoint were cancer [OR: 3.07 (1.22–7.85)]; renal insufficiency at admission [OR: 2.53 (1.17–5.8)]; persistent signs of RVD at 48 h echography [OR: 3.99 (1.36–11.3)]. The severity of RPVO at discharge was significantly associated with an unfavourable outcome [OR: 2.66 (1.58–3.93)]. Note that patients with RPVO greater than threshold at discharge had a significantly higher risk of death at 6 months ($P = 0.01$).

Begic *et al.*[35] evaluate through serial V/Q SPECT examinations over a 6 month period. The treating pulmonologist decided to terminate therapy in 35 (73%) patients and to continue anticoagulant (AC) in 13 patients because of persistent risk factors. Six months later, at the second control stage, 53 (82%) patients had complete recovery of pulmonary perfusion. Eleven patients still had perfusion defects at 6 months. No recurrence was identified at 6 months in the 35 patients whose therapy was terminated after 3 months. No bleeding effects were observed in any of the patients during the 6 month FU. The authors assessed that anticoagulant therapy can be tailored by using V/Q SPECT. Normalization of perfusion at 3 months of initial PE diagnosis was a reliable indicator that the treatment could be safely withdrawn in patients who were without hypercoagulability risk.

Stein *et al.*[36] retrospectively assessed the rate of resolution of pulmonary emboli in individual vessels and the rate of complete resolution of PE on CT angiography. In particular, complete CT angiographic resolution of PE was seen in 6 of 15 patients (40%) 2–7 days after diagnostic imaging. After Day 28, complete resolution occurred in 17 of 21 patients (81%). On the contrary, Miniati *et al*[37] prospectively evaluated 834 consecutive patients with a scintigraphic FU in order to evaluate the restoration of pulmonary perfusion over a 1-year period. Complete resolution of PE by lung scanning was observed in 65% of patients after 1 year. A lower rate of normalization was observed by Wartski *et al.*[38] (34%). In a prospective series of 254 patients with confirmed PE, Sanchez *et al.*[39]

Table 3 Recommendations for TTE

Transthoracic echocardiography (TTE) is useful to assess the presence of pulmonary arterial hypertension (PAH). However, the gold standard technique remains the cardiac catheterization.
TTE should always be performed at discharge to evaluate PAH and if present, FU at 3 and 6 months must be considered;
TTE follow-up should be considered only for those patients with a right ventricle–right atrium (RV–RA) gradient >45 mmHg or in the presence of both dyspnoea and a RV–RA gradient ranging between 32 and 45 mmHg at discharge.

Table 4 Recommendations for magnetic resonance imaging, computed tomography, and lung scintigraphy

Lung perfusion scan must be performed 3 months after the acute event in those patients with persisting symptoms and/or in the presence of right ventricular dysfunction or pulmonary artery hypertension
Computed tomography is not useful to redefine therapeutic strategies during the follow-up
Pulmonary RMI is not useful during venous thromboembolism follow-up.

MRI: magnetic resonance imaging.

highlighted with V/Q scan that 29% of subjects had perfusion defects during FU (median 12 months) and were more likely to have dyspnoea, higher systolic PAP, and walked a shorter distance during the 6MWT. Nijkeuter *et al.*[40] described that the percentage of patients with residual pulmonary thrombi was 87% at 8 days after diagnosis, 68% after 6 weeks, 65% after 3 months, 57% after 6 months, and 52% after 11 months.

Alhadad *et al.*[41] identified that patients with persistent perfusion defects at the FU SPECT have a high risk of PE recurrence. In particular, 16% had recurrent PE, and of these, 34 (92%) showed residual perfusion defects at the second V/P SPECT.

Den Exter *et al*[42] in their prospective multicentre study analysed 157 patients with acute PE and evaluated the routine use of FU CT pulmonary angiography (CTPA) imaging. After 6 months of treatment, complete PE resolution occurred in 84.1% of the patients [95% confidence interval (CI): 77.4–89.4%]. During FU, 16 (10.2%) patients experienced recurrent VTE. However, the presence of residual thromboembolic obstruction resulted not associated with recurrent VTE (adjusted HR: 0.92; 95% CI: 0.2–4.1). These findings confirmed that the routine use of FU CTPA imaging in patients treated for acute PE is not useful in clinical practice. Interesting results will come from the Italian study SCOPE 2 (Study on the clinical Course Of Pulmonary Embolism), realized by Raffaele Pesavento and Paolo Prandoni. These researchers are searching for a possible correlation between embolic residual (evaluated with perfusion scans after six months from the acute event) and the development of symptomatic recurrent PE and/or CTPEH.

Table 4 summarizes the recommendations for MRI, CT, and LS.

Right heart catheterization and haemodynamic evaluation

Despite recent progress in imaging techniques, RHC[43–45] is required to confirm the diagnosis of PAH and CTEPH, to assess the severity of haemodynamic impairment, to undertake vasoreactivity testing of the pulmonary circulation in selected patients, and to support treatment decisions.[46] Despite clinical symptoms and signs are non-specific or absent in early CTEPH, those patients that during FU developed clinical symptoms compatible with PAH must be evaluated. Diagnosis of CTEPH is based on the findings obtained after at least 3 months of effective anticoagulation, in order to discriminate this condition from 'subacute' PE.

For the diagnosis of CTEPH, mean pulmonary arterial pressure (mPAP) must be ≥25 mmHg, with pulmonary artery wedge pressure (PAWP) ≤15 mmHg and the pulmonary vascular resistance (PVR) ≥3 Wood units (WU); in addition, at least one (segmental) perfusion defect detected by perfusion lung scan or pulmonary artery (PA) obstruction seen by CT angiography must be present (*Table 5*).[30]

Digital subtraction pulmonary angiography is used to define the extension and distribution of the thromboembolic disease highlighting the features of angiographic signs.[47]

Contrast volume used during angiography should be tailored on the basis of the patient's weight and cardiac output, in order to obtain excellent images minimizing the risk of contrast-induced nephropathy. It must be considered that poor subpleural perfusion in the capillary phase of pulmonary angiography might be related to small vessel disease and a poor surgical outcome of CTEPH.[48] The operability of patients with CTEPH is determined by multiple factors that cannot easily be standardized; these are related to the suitability of the patient, the expertise of the surgical team, and available resources. Coronary angiography may be required in the presence of angina, risk factors for coronary artery disease, and listing for PEA.[43]

Both the extent of proximal occlusion of PAs and secondary small-vessel arteriopathy contribute to the elevated pulmonary vascular resistance. High pressure, high shear stress, inflammation, and an imbalance of vasoactive mediators result in vascular remodelling, including the formation of plexiform lesions.[49] Finally, the presence of high pulmonary vascular resistance compared with the degree of vascular obstruction is an indirect sign of high operative risk and, in some cases, of inoperability (small vessel disease).[50] Indeed, postoperative pulmonary vascular resistance predicted in-hospital and 1-year mortality. The last ESC guidelines[31] on PAH recommended that pulmonary vasoreactivity testing, for identification of patients suitable for high-dose calcium channel blocker treatment, is recommended only for patients with idiopathic PAH, heritable PAH, or drug-induced PAH. It should be performed at the time of RHC. On the contrary, some authors verified that

Table 5 Right heart catheterization in chronic thromboembolic pulmonary hypertension

Haemodynamic parameters
mPAP $\geq$25 mmHg
PAWP $\leq$15 mmHg
PVR $>$ 3 WU
Pulmonary angiography
Pulmonary arteries dilatation
Vascular obstruction
Vascular webs
Post-obstructive dilatation
Pulmonary areas of reduced perfusion

mPAP, mean pulmonary arterial pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; WU, Woods units.

acute vasoreactivity identifies CTEPH patients prone to develop persistent/recurrent PH after PEA.[51]

Functional test: the 6-minute walking test and cardiopulmonary exercise testing

After the acute phase of PE, patients can be divided into three different groups: patients with complete resolution of the thrombus, with chronic thromboembolism without PAH, and with chronic thromboembolism associated with CTPEH (Group IV of OMS classification of PH). The latter group represents the 3.8% of all acute PE.[52,53] Diagnosis in these patients must be performed as soon as possible. However, the assessment of this condition with non-invasive tests, nowadays, remains a challenging issue. Moreover, most part of scientific evidences have posed their attention on the role of different functional tests in the prognosis stratification but not during the FU of PE.

The common pathophysiological basis as well as the microvascular inflammatory remodelling as stated in the European guidelines could allow to transfer the interpretation of the test utilized in the PAH also in the CTEPH.[31,54]

Pulmonary hypertension is likely to persist as well after PEA in patients with significant small-vessel arteriopathy, resulting in poor clinical outcome and increased perioperative mortality. The 6MWT remains the most widely used exercise test in PH centres. Indeed, it is easy to perform, inexpensive, and familiar to patients and centres.

The assessment of functional capacity by cardiopulmonary exercise testing (CPET) seems to be more complete, because CPET allows a discrimination between the metabolic, cardiovascular, and pulmonary components of exercise limitation. Moreover, CPET estimates the severity of disease and assesses patients' prognosis and response to therapy.[55]

Despite there are no definitive data on the use of functional tests in the PE FU, we suggest that both tests can be used in CTEPH as in PAH patients; symptoms and the patient's functional status must be the main determinant in the clinical decision-making regarding both the most appropriate therapeutic timing and instrumental strategy *Table 6*.[56-60]

Evaluation of post-thrombotic syndrome

Post-thrombotic syndrome is a problem that can develop in nearly half of all patients who experience a DVT in the leg. Most common symptoms are oedema (typically pronounced at the end of the day or after prolonged standing and/or walking), pain, hyper-pigmentation, and skin ulcers. Although recommended by guidelines, appropriate DVT prophylaxis remains considerably underused. Increasing the awareness of PTS and the methods to prevent this complication may help reduce its incidence, improve long-term outcomes in patients, and decrease resulting costs associated with treatment.[61-64] It is estimated that the quality of life is worse compared with patients with other chronic diseases.[65] In a prospective study of 387 patients, who received an objective diagnosis of acute symptomatic DVT, about half of the cases have developed PTS. Severe PTS was registered in only 2% of patients.[66] Some studies report that the cumulative incidence of PTS continues to increase also after 2 years up to 10 to 20 years from the acute episode.[67,68]

Pathogenesis and risk factors: In the pathogenesis of PTS a central role is played by the increase in pressure in the lower limb venous system, determined by two factors:

(1) Venous valvular damage and persistent luminal obstruction.
(2) after DVT, recanalization of the thrombosed veins, is often incomplete.[64,65] Indeed, as demonstrated by Prandoni *et al.*[67,68], the lack of recanalization within the first 6 months after the thrombotic episode is an important predictor of PTS, while the development of trans-popliteal venous reflux is not.

It must also be considered that a significant association between markers of inflammation, such as IL-6 and ICAM-1, and the development of PTS exists.[69,70]

A number of clinical tools or scales have been used to help diagnose and define PTS. Of these, three were developed specifically to diagnose PTS after objectively diagnosed DVT: the Villalta scale, Ginsberg measure, and Brandjes scale. The others, developed for chronic venous disease in general, include the CEAP (clinical, aetiological, anatomic, pathophysiological) classification, Venous Clinical Severity Score (VCSS), and Widmer scale. The Villalta scale has been widely and successfully used to diagnose PTS, to classify its severity, and to evaluate treatment, including in randomized controlled trials (RCTs). CEAP is not an ideal scoring system to diagnose and FU the course of PTS.[71,72]

Risk factors for developing PTS are older age, elevated body mass index, and obesity.[62,63,66,67,69] Recurrent ipsilateral DVT has been shown in numerous studies to be an important risk factor for PTS. The variability in the magnitude of effect across studies (ORs: 1.6–10) is probably attributable to differences in study populations and definitions of PTS. However, all are consistent in showing ipsilateral recurrence to be predictive of future PTS.[73]

Prevention and treatment of PTS: Because PTS is a consequence of DVT and thromboprophylaxis is an effective means of preventing DVT, it is clear that use of pharmacological or mechanical thromboprophylaxis in high-risk

Table 6 Timing of clinical evaluation and functional test in patients with chronic thromboembolic pulmonary hypertension

	At baseline	Every 3–6 months	In case of change in therapy or after PEA	In case of clinical worsening
Clinical assessment and functional class	✓	✓	✓	✓
6MWT	✓	✓	✓	✓
CPET	✓		✓	✓

6MWT, 6-min walking test; CPET, cardiopulmonary exercise testing; PEA, pulmonary endarterectomy.

patients and settings as recommended in evidence-based consensus guidelines will prevent cases of PTS. Recently, a Scientific Statement from the American Heart Association (AHA) on PTS has evidenced that the use of thromboprophylaxis in patients at significant risk for DVT is recommended as a means of preventing PTS (Class I; Level of Evidence C).[63] Moreover, anticoagulation of appropriate intensity and duration for treatment of the initial DVT is recommended as a means of reducing the risk of recurrent ipsilateral DVT and consequent PTS (Class I; Level of Evidence B). Surgical thrombectomy might be considered in selected patients with extensive acute proximal DVT who are not candidates for anticoagulation because of bleeding risk.[65,74,75]

Graduated stockings (GS), intermittent compression, and medical treatment are the cornerstone in the treatment of PTS.[65]

Two small, randomized trials comprising a total of 115 patients have evaluated the ability of 30–40 mmHg GS to reduce symptoms in patients with PTS.[76,77] American College of Chest Physicians (ACCP) recommended (Grade 2B recommendation) GS in acute symptomatic DVT,[9] while although more recently the SOX study has demonstrated that GS did not prevent PTS after a first proximal DVT.[78] The aforementioned AHA Scientific Statement AHA recommends the use of GS (Grade IIB), despite the methodological limitations and statistical imprecision that preclude confident conclusions about their effectiveness in patients with PTS.[65,78]

Objective risk stratification of PTS, using colour Doppler ultrasound for evaluating recanalization and reflux and D-dimer testing, must be an integral part in routine clinical practice to assess the optimal duration of wearing medical elastic stockings and anticoagulation for the prevention DVT recurrence as the best option to reduce the incidence and costs of suffering from irreversible PTS. Palareti *et al.*[79] have evaluated the predictive value of D-dimer for the risk of VTE recurrence after oral anticoagulant therapy (OAT) withdrawal. The main result of the study was that D-dimer has a high negative prognostic value for VTE recurrence when performed after OAT discontinuation.[79–82] Conversely, Latella *et al.*[83] showed that D-dimer levels, measured 4 months after DVT in patients not on warfarin, are associated with subsequent development of PTS. Different results were presented in the PROLONG study, which concluded that patients with an abnormal D-dimer level 1 month after the discontinuation of anticoagulation have a significant incidence of recurrent VTE, which is reduced by the resumption of anticoagulation[82] Other important suggestions have been provided by the CFCA guidelines.[20] Indeed, authors recommended a prolonged anticoagulation in patients with idiopathic venous thromboembolic, especially in the case of recurrent episodes or active malignancy. Based on persistently normal D-dimer tests, anticoagulation could be stopped in >50% of the patients included after a single idiopathic VTE or associated with sodium warfarins (*Table 7*).[84]

Residual venous thrombosis of the lower limbs

Different Italian studies have demonstrated that residual venous thrombosis is an important risk factor for recurrent thromboembolism. Ultrasonographic assessment of residual venous thrombosis may help clinicians to modify the duration of anticoagulation in patients with DVT.[85,86] The hazard ratio for recurrent thromboembolism was 2.4 (95% CI: 1.3–4.4, $P = 0.004$) for patients with persistent residual thrombosis vs. those with early vein recanalization. Subsequent randomized studies have suggested that tailoring the duration of anticoagulation on the basis of ultrasonography findings reduces the rate of recurrent VTE in adults with proximal DVT.[87,88] However, a recent meta-analysis has evidenced that residual venous obstruction (RVO) was independently associated with recurrent VTE (HR = 1.32, 95% CI: 1.06–1.65). The association was stronger if RVO was detected early, i.e. at 3 months after DVT (HR = 2.17; 95% CI: 1.11–4.25), but non-significant if detected later, i.e. >6 months (HR = 1.19; 95% CI: 0.87–1.61)[89] The studies reviewed were heterogeneous not only in the timing of the ultrasound evaluation but also in the definition of residual thrombus.

The measurement of residual vein diameter, as the main characteristic for diagnosing an ipsilateral recurrent DVT, in a previously abnormal segment must be performed. We suggest evaluation of the increase in residual vein diameter in popliteal and femoral veins. If the vein diameter is >4 mm, the patient should be treated for a recurrent ipsilateral proximal DVT; if 2–4 mm, we recommend that ultrasonography with simplified compression be repeated after 7 days and that treatment be initiated if the diameter is >4 mm at this time; if <2 mm, we suggest further imaging test at 7 days only in patients with a high clinical probability of recurrence.[90]

Residual thrombosis of the pulmonary arteries

As previously mentioned, we suggest that CTPA or lung scan should not be routinely performed in all patients with a

Table 7 Recommendation for preventing post-thrombotic syndrome

It is mandatory to assess patient with deep vein thrombosis with both Villalta and CEAP scoring system after 1, 3, 6, and 12 months.
An accurate diagnosis of post-thrombotic syndrome can be made only after 3–6 months after the acute event
All patients who developed symptoms, which not disappear at rest, suggestive of venous thromboembolism during follow-up must be evaluated to exclude a deep vein thrombosis
Physician, during venous thromboembolism follow-up must recommend to patients: • Weight loss; • Compliance with anticoagulation treatment; • International normalized ratio assessment during vitamin K antagonists treatment; • Attention to new symptoms and eventually evaluate the presence of lung and/or peripheral thrombotic residual.

previous episode of PE for the research of residual thrombosis of the PAs because of its lack of prognostic and therapeutic information. However, it may be considered in those thought to be at high risk for recurrence.[91]

Co-morbidity: cancer and autoimmune diseases

Cancer

An association between VTE and cancer has been previously suggested; the overall risk of VTE in cancer patients is four times as great as in the general population. Sometimes malignancy could be the first and only clinical presentation of VTE. Tumour cells can express everything required for regulation of the fibrinolytic pathway on their cell surface. The expression of tissue factor on tumour cells and the prothrombotic properties of mucins contribute to the thrombosis risk in malignancy. In addition, there is evidence that tissue factor expression, which may result from proto-oncogene expression and tumour suppressor gene inhibition, confers a pro-angiogenic state, which may enhance the aggressiveness and invasiveness of cancer.[100] Indeed, tumour cells are known to carry the specific PA receptors (u-PAR) on their membranes, which can facilitate the activation of the fibrinolytic system. The prevalence of previously undiagnosed cancer in patients with unprovoked VTE has been estimated in previous studies: 6.1% (95% CI: 5.0–7.1%) at baseline and 10.0% (95% CI: 8.6–11.3%) from baseline to 12 months. Moreover, cancer is more prevalent in patients with bilateral DVT, early VTE recurrence, or very high D-dimer.[92–97] After the first year, the number of diagnoses is close to that of the general population, although some population studies show the persistence of an increased risk of developing cancer.

A systematic review of 15 studies, published in 2008, affirmed that previously undiagnosed cancer was frequent in patients with unprovoked VTE. For this reason, an extensive cancer screening strategy could be able to detect more malignant conditions than a limited screening strategy does.[92] This strategy is fundamental to choose the correct anticoagulant treatment in these patients. Conversely, the utility of screening for cancer in VTE patients is controversial. Routine screening with CT of the abdomen and pelvis did not provide a clinically significant benefit in these patients. Studies published until 2014, designed to evaluate the efficacy of an extensive cancer screening, were characterized by methodological heterogeneity and a relatively small number of subjects enrolled. In fact, the largest study enrolled only 396 patients.[98–101] Previous studies have several limitations: in particular, the real incidence between asymptomatic cancer at early stages is very difficult to assess, due to the retrospective design of the studies.

Further investigations for cancer have been suggested in the 2012 NICE guidelines; abdomino-pelvic CT scan (and a mammogram for women) should be performed in all patients aged over 40 years with a first unprovoked DVT or PE who do not have signs or symptoms of cancer based on initial investigation.[102] In the last Italian guidelines of Italian Association of Medical Oncology, published in 2015,[103] authors recommend to suspect an occult malignancy in all patients with first idiopathic VTE and to perform in these subjects a routine screening on the basis of current clinical practice (Level of evidence D; recommendation: Positive low). British Committee for Standards in Haematology (BCSH) affirmed that in patients aged above 40 years with unprovoked VTE, screening for cancer with CT scan (and mammography for women) should be considered but not routinely performed (levels of recommendation 2C).[100]

Recently, interesting data have been presented in The Screening for Occult Malignancy in Patients with Idiopathic Venous Thromboembolism (SOME).[104] This trial was a multicentre, open-label, RCT comparing an extensive screening comprehensive CT of the abdomen and pelvis in addition to limited occult-cancer screening vs. limited occult-cancer screening alone in patients with unprovoked VTE. Patients assigned to the limited screening strategy underwent a complete history taking and physical examination, measurement of complete blood counts and serum electrolyte and creatinine levels, liver function testing, and chest radiography. Sex-specific screening was conducted if it had not been performed in the previous year. A breast examination, mammography, or both were performed in women older than 50 years of age, and Papanicolaou (Pap) testing and a pelvic examination were performed in women aged 18–70 years who had ever been sexually active. A prostate examination, prostate-specific antigen test, or both were performed in men older than 40 years of age. Patients assigned to limited screening plus CT also underwent

comprehensive CT of the abdomen and pelvis. Moreover, CT included a virtual colonoscopy and gastroscopy, biphasic enhanced CT of the liver, parenchymal pancreatography, and uniphasic enhanced CT of the distended bladder. Of the 854 patients in the intention-to-test population, 33 (3.9%; 95% CI: 2.8–5.4) received a new diagnosis of cancer in the interval between randomization and the 1-year FU. The diagnosis of occult cancer between limited screening group and limited screening plus CT was not statistically different. Furthermore, after the completion of the initial screening, the absolute rates of occult-cancer detection were 0.93% (95% CI: 0.36–2.36) with the limited screening strategy and 1.18% (95% CI: 0.51–2.74) with the strategy of limited screening plus CT (absolute difference, 0.25 percentage points; 95% CI: −1.12 to 1.63). Then after the completion of the initial screening, the absolute rates of occult-cancer detection were 0.93% (95% CI: 0.36–2.36) with the limited screening strategy and 1.18% (95% CI: 0.51–2.74) with the strategy of limited screening plus CT (absolute difference, 0.25 percentage points; 95% CI: −1.12 to 1.63). These results confirmed that routine screening with CT of the abdomen and pelvis did not provide a clinically significant benefit in patients with a first episode of idiopathic VTE.

Considering nuclear medicine techniques, some studies confirmed that a diagnosis strategy, based on positron emission tomography–CT screening for malignancy in patients with unprovoked VTE had limited diagnosis value and may lead to unnecessary alarming and money- and time-consuming investigations.[105,106]

We suggest that screening strategy for occult-cancer, which included clinical evaluation, laboratory tests, chest X-ray, and comprehensive CT of the abdomen and pelvis in patients who had a first unprovoked VTE, should be considered. The decision to proceed with an extensive screening should be evaluated case by case

Autoimmune diseases

Autoimmune disorders such as systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), and Behçet's syndrome have been linked to an increased risk of VTE.[107-112] Moreover, in recent years, also patients with rheumatoid arthritis, celiac disease, hyperthyroidism, and Wegener's granulomatosis had an elevated risk for VTE.[113-116] The link between autoimmune disorders and VTE have not been completely clarified.

However, many studies have established the association between inflammation and the hypercoagulable state or between inflammation and endothelial dysfunction in VTE.[117]

It has been hypothesized that anti-protein S (anti-PS) antibodies, independently of antiphospholipid antibodies (aPL), may play a role in the occurrence of PS deficiency in some patients with SLE, with possible effects on the function of PS that do not change the levels of PS antigens.[118,119]

Antiphospholipid antibodies, in fact, are commonly found in patients with autoimmune diseases. It has been estimated that immunoglobulin G anticardiolipin antibodies (aCLs) could be found in 33% of patients with SLE, 17% in systemic vasculitis, 25% in thrombotic thrombocytopenic purpura, 24% in thyroid disease, in haemolytic autoimmune anemia, and in 16% of patients with rheumatoid arthritis.[120-125] Thrombosis has been reported in about 10–26% of patients with SLE; moreover, these subjects had a VTE risk of three-fold higher respect than the normal population.[126-132] On the contrary, patients with other autoimmune diseases, such as trombocytopenic thrombotic purpura, polyarteritis nodosa, polymyositis, and dermatomyositis had six-fold higher risk for VTE.[133] Currently, there is no conclusive evidence about routine screening of autoimmune disease during VTE. Once again the International Society on Thrombosis and Haemostasis (ISTH), the British Committee for Standards in Haematology (BCSH), and the Clinical and Laboratory Standards Instituite (CLSI) have recommended testing for aPL in patients with unprovoked proximal DVT or PE after stopping anticoagulation (for at least 7 days) as the presence of aPL will influence the balance of risks and benefits and support long-term anticoagulant therapy.[134-136]

Overview of medical and surgical therapy

Anticoagulants and antiplatelet drugs (traditional therapy)

Anticoagulants

Anticoagulation is the mainstay of treatment for VTE.

Conventionally anticoagulation therapy could be divided into three phases:

(1) An acute phase (conventionally the first 7 days), with the objective of limiting the extension of thromboembolism and preventing early death and recurrent symptomatic or fatal VTE.
(2) A long-term phase in which prevention of new episodes of VTE predominates.
(3) An extended period (indefinite), in which anticoagulation is continued for over 3 months without a scheduled stop date. The indefinite anticoagulation should be reserved to those patients with high risk of recurrence.

At the end of the active phase of treatment, therapeutic decisions are based on patient's risk factors (presence of cancer, obesity, male, and idiopathic VTE), previous clinical history (thrombotic or haemorrhagic disease in the past, provoked, or unprovoked VTE), diagnostic assessment (thrombotic burden and persistence of RVD or PH), laboratory markers (D-dimer or thrombophilic mutations),[11,89] and the balance between the risk of bleeding and the advantage of preventing the recurrence of the VTE.

Oral anticoagulation: vitamin K antagonists

Oral anticoagulation with VKAs requires an individual identification of optimal dosage monitoring the international normalized ratio (INR) levels aiming for an INR level of 2.0–3.0. A lower intensity of anticoagulation (INR < 2) is associated with a greater likelihood of recurrent thromboembolic events, while a more intense anticoagulation is associated with the occurrence of bleeding events.[139]

The long-term treatment with warfarin is effective in preventing recurrent VTE.

Recurrency, despite VKA therapy, occurs in about 2% of patients.

Parenteral anticoagulation: low-molecular-weight heparin

Previous studies in patients with cancer and acute VTE have demonstrated that dalteparin was more effective than oral anticoagulant in reducing the risk of recurrent VTE, without increasing the risk of bleeding.[137,138,140] In patients with cancer and acute PE, low-molecular-weight heparin administered in the acute phase (except for high-risk PE) and continued over the first 3–6 months should be considered as first-line therapy. For patients with PE and cancer, extended anticoagulation (beyond the first 3–6 months) should be considered for an indefinite period or until the cancer is cured. Incidence of recurrent provoked VTE (due to surgery, trauma, immobilization, pregnancy, and hormonal replacement therapy) is estimated at almost 5% per year. However, among those patients, the incidence of recurrence seems to be lower in the case of previous surgery. In the unprovoked forms, the incidence of recurrent VTE is approximately 15%.[141,142]

Antiplatelet agents

In patients who refuse to take or are unable to tolerate any form of oral anticoagulants, aspirin could be considered for extended secondary VTE prophylaxis. In two recent trials, ASPIRE[142] and WARFASA,[143] extended therapy with aspirin (after termination of standard oral anticoagulation) was associated with a 30–35% reduction in the risk of recurrence after unprovoked without increasing the risk of bleeding events.

New oral anticoagulants for extended treatment

Nowadays, new oral anticoagulants (NOACs) have been evaluated both in first phases and in the extended treatment of patients with VTE.

Four NOACs have been evaluated for VTE treatment: dabigatran (an oral thrombin inhibitor) and rivaroxaban, apixaban, and edoxaban, which are oral factor Xa inhibitors. All four agents have been compared with conventional anticoagulant therapy for the treatment of acute symptomatic VTE, and all but edoxaban have been compared with placebo for extended treatment.[144–149]

These studies have some common characteristics:

- Inclusion criteria (age >18 years, a confirmed and previously treated VTE);
- Exclusion criteria (anticoagulant treatment for other diseases, dual antiplatelet therapy, thrombocytopenia, anaemia, renal function-estimated with glomerular filtration rate <25 mL/min or serum creatinine >2.5 mg/dL, hypertransaminasaemia, and higher bilirubin levels).
- The endpoint: recurrent VTE, mortality for all causes and PE related).

Safety of treatment was labelled as a haemoglobin drop ≥2 g/dL, requiring blood transfusion and minor bleeding events. To notice the concept of 'clinically relevant bleeding', this one was defined as the need for medical intervention (unlike the previous definitions of major or minor bleeding events). Two-thirds of patients enrolled had a VTE, while a third had only PE. Except for the REMEDY trial in which Dabigatran was compared with warfarin,[184] others studies compared NOACs with placebo. The characteristics of the enrolled populations were similar to those represented in the VTE registry but younger in age, with less co-morbidities and a low prevalence of active cancer; however, a greater number of idiopathic PE was recorded.

The results of the aforementioned studies could be summarized as follows:

- Patients treated with placebo, despite less serious VTE respect to patients commonly treated in daily clinical practice, had a higher rates of recurrent VTE (up to 8.8%);
- Treatment reduced the rates of recurrent VTE; however, a higher prevalence of bleeding events was recorded.
- A single study demonstrated that dabigatran was effective in the extended treatment of VTE and carried a lower risk of major or clinically relevant bleeding than warfarin but a higher risk than placebo.[150]
- The rates of bleeding have not been widely investigated in previous studies during the extended phase of treatment.

However, daily clinical practice demonstrated that bleeding events are more frequent than the estimation performed in clinical trials. RESONATE trial shows that treatment efficacy continues even after treatment withdrawal.[151] These evidences indicate that NOACs are useful in the extended phase of treatment, especially in patients at higher risk of recurrent VTE with a relative low risk of bleeding.

Clinical trials have been performed with a view to making significant changes to the acute, long-term, and extended treatment of VTE.[152] ESC guidelines recommend that the administration of one of the new oral anticoagulants such as dabigatran, apixaban, or rivaroxaban should be considered as an alternative treatment in VTE. However, NOACS are not recommended in patients with severe renal impairment (evidence level IIa B),[2] during pregnancy, breastfeeding, and severe liver disease associated with significant bleeding risk (CHILD PUGH B and C).

Duration of the treatment

Whatever the choice of anticoagulant, the standard duration of therapy should cover at least 3 months. After withdrawal of anticoagulant treatment, the risk of recurrence, if anticoagulants are stopped after 6 or 12 months can be expected to be similar to that after 3 months. On the contrary, an indefinite treatment reduces the risk for recurrent VTE by about 90%, but this benefit is partially offset by a 1% or higher annual risk of major bleeding.[153]

There are no properly evaluated bleeding risk scores for patients receiving anticoagulant treatment for VTE. Based on currently available evidence, risk factors include age

>75 years, previous gastrointestinal bleeding, previous stroke (either haemorrhagic or ischaemic), chronic renal or hepatic disease, concomitant antiplatelet therapy (must be avoided, if possible), other serious acute or chronic illness, poor anticoagulation control, and suboptimal monitoring of anticoagulant therapy.

The indefinite duration of anticoagulation should be considered in all the patients in which an unprovoked VTE has been diagnosed or in high-risk provoked cases; in these patients, the option to withdraw anticoagulant treatment should periodically be reassessed, considering the dynamic balance between the risks of recurrence and bleeding.

Whenever the anticoagulation is abandoned, the patient should be followed for a time sufficient to redefine his/her risk of recurrence (6–12 months).

Venous filters (inferior vena cava)

Venous filters are indicated in patients with acute PE who have absolute contraindications to anticoagulant drugs and in patients with objectively confirmed recurrent PE despite adequate anticoagulation treatment.[2,9,154] The frequency of inferior vena cava (IVC) filter placement has doubled over the past decades,[155,156] especially after the introduction of retrievable filters and more complex and smaller devices generating more indications for their use.

Nevertheless, current clinical evidence supporting the use of the venous filters are limited. In fact, categories of patients with PE in whom vena cava filters reduce in-hospital case fatality rate have not been definitively assessed.[156] Stein *et al.*,[157] in 2012, observed that patients who received a vena cava filter had a lower case fatality rate than those who did not; moreover, unstable patients who received thrombolytic therapy had a lower in-hospital case fatality rate with vena cava filters than those who did not.

The latest European guidelines on PE published in 2014 have stated that IVC filters in patients with PE is not recommended.[2] Indeed, IVC should be considered only in those patients who have an absolute contraindication to anticoagulation therapy, or in case of recurrent VTE, despite therapeutic levels of anticoagulation.

Previous evidence has already demonstrated the utility of placement of an IVC filter for recurrent thromboembolism that occurs despite adequate anticoagulation, for chronic recurrent embolism with PH, and with the concurrent performance of surgical pulmonary embolectomy or pulmonary thromboendarterectomy (Grade 1C).[158,159] Broader indications have also been provided by single studies on other clinical conditions such as malignancies, recent trauma, acetabular fractures, and after orthopaedic surgery placement of joint, and hip or knee prosthesis. The lack of definitive recommendations on IVC filters could be due to the fact that most of the survival data derived from observational studies performed in small cohorts. Only few randomized trials have been performed with the aim to clarify the role of IVC in clinical practice. The PREPIC study was the first randomized trial that studied both the efficacy and the safety of vena cava filters in the prevention of PE in patients with proximal DVT. Using a two-by-two factorial design, 400 patients with proximal deep-vein thrombosis who were at risk for PE received a vena cava filter (200 patients) or no filter (200 patients). At 2 years, 37 patients assigned to the filter group (20.8%), when compared with 21 patients assigned to the no-filter group (11.6%), had recurrent DVT (OR: 1.87; 95% CI: 1.10–3.20). No significant differences in mortality were recorded.[160] At 8 years, vena cava filters reduced the risk of pulmonary embolism but increased that of deep-vein thrombosis and had no effect on survival.[161] Instead, the PREPIC-2 FU among hospitalized patients with severe acute PE, the use of a retrievable IVC filter plus anticoagulation compared with anticoagulation alone did not reduce the risk of symptomatic recurrent pulmonary embolism at 3 months[162]. Schuun *et al.*[163] have shown a higher survival in those patients who had placed an IVC filter compared with subjects who received anticoagulation (18.5 vs. 12.8%). Ihnat *et al.*[164] showed no significant differences after 1 year for patients treated with filter and anticoagulation therapy (35 vs. 38%, P = ns). Kucher *et al.*[165], among 2392 patients with PE, described that none of the patients who received an IVC filter developed recurrent PE within 90 days, and 90.9% survived at least 90 days. On the contrary, 90 day survival rates were 79.1% in patients with an IVC filter and 86.0% in those without an IVC filter (HR: 1.50; 95% CI: 1.10–2.04; $P = 0.009$).

The main indications for implantation of a vena cava filter in the presence of VTE are:

a. proven VTE with contraindications for anticoagulation;
b. proven VTE complications of anticoagulation treatments; and
c. recurrent VTE despite anticoagulation treatment.

Actually there are no definitive data about the use of IVC filters in the prophylaxis of VTE in patients at high risk (i.e. patients with multiple trauma); moreover, their use is not recommended in patients who may be treated with anticoagulation.

Imberti *et al.*[166] in a recent consensus paper provide evidence and clinical judgements describing the management of patients with IVC filters (*Table 8*).

Complications arising from the placement of vena cava filters

Complications may occur during IVC placement, after interventional procedure, but also in the long-term period after many years. Intra-procedural complications are relatively rare and may result from malposition of the device (1.3%), air embolism (0.2%), pneumothorax (0.02%), and inadvertent carotid puncture (12.04%).[167,168] A relatively frequent complication in the post-interventional period is represented by the thrombosis at the insertion site (10.8%).[169,170] Delayed complications, including filter fracture, migration, IVC thrombosis, and recurrent PE, and complications of filter retrieval after implantation of temporary IVC filters have also been described.

Vena cava filters in cancer patients

Patients with cancer had twice the incidence of VTE, PE, and DVT as patients without cancer. Many recent studies questioned the need to insert IVC filters in advanced-stage cancer patients, particularly those whose anticipated

Table 8 Management of patients with vena cava (inferior vena cava) filters

There is no evidence to support the hypothesis that inferior vena cava (IVC) filters reduce death from acute VTE
Available evidence shows no short-term or long-term mortality benefit from IVC filter placement plus anticoagulation (compared with anticoagulation therapy alone).
It is not known whether IVC filters would reduce death in patients with acute VTE compared with no treatment
IVC filters, when used in patients with acute DVT, are associated with an increased risk of PTS
Patients with IVC filters should remain on anticoagulant therapy as long as: a. the filter remains in place, b. the therapy is well tolerated, and c. the proportion of time in the therapeutic range is high.
Filters should be removed at the earliest possible time, ideally within weeks and not later than 120 days from their insertion. Delaying removal probably reduces the likelihood of removal and the duration of 'safe removal' is probably also a function of the type of filter.

survival is short and prevention of PE may be of little clinical benefit and could be a poor utilization of resources. Conflicts have been reported about the indication and appropriate timing to place IVC filters in cancer patients. However, these data cannot be considered in current medical practice, because patients were not stratified according to the current PE classifications; indeed, PE was defined through both anatomical and angiographic criteria (Miller index or lung scan). Despite that, some useful recommendations have been proposed in recent studies. In fact, haemodynamically stable patients with PE and solid malignant tumours who were aged >30 years appeared to be a subset of patients with PE who would benefit from vena cava filters.[171]

Elastic compression stockings

Graduated elastic compression stockings (GECS) help prevent DVT and more in general VTE by applying varying amounts of pressure to different parts of the leg. The PTS is a chronic condition that develops in 20–50% of patients with DVT.[9,172-173] The main risk factors for PTS are persistent leg symptoms 1 month after acute DVT, anatomically extensive DVT, recurrent ipsilateral DVT, obesity, and older age.

Previous studies on GECS have enrolled surgical patients in most cases. We can divide these studies respect to their endpoints:

- studies about clinical efficacy and
- studies about haemodynamic effectiveness

Graduated compression stockings or elastic-compressive bandage (GCES) reduce the overall cross-sectional area of the limb, increase the linear velocity of venous flow till five times, reduce venous wall distension, and improve valvular function. Arterial disease may contraindicate the use of compression therapy. The Italian Society of Phlebology.[174] recommends to use of GECS with caution if there is an arterial ankle–brachial index (Winsor index) <0.8.

The use of Class 3 stockings during the 15–20 days after the acute event is able to reduce the incidence of PTS of 50%.[9,77,172,173]

The cumulative incidence of the post-thrombotic syndrome in the control group vs. the elastic stockings group was 49.1% vs. 24.5% (CI: 15.6–33.4%) after 2 years. However, there are some areas of uncertainty about the use of GECS. Partsch *et al.*[175] demonstrated in their study that immediate mobilization with compression in the acute stage of DVT reduces the incidence and the severity of PTS. However, one important limitation was that the bandage procedures required skilled personnel. The same authors have also demonstrated that the use of Class 2 stockings modified over time according to the clinical evolution of the disease was related to a rapid reduction of thrombus size measured at venous Duplex.

Actually, there are no definitive data regarding the role of GCES in the dissolution of the residual thrombus.

The recommendations for the use of GCES are summarized in *Table 9*.

Surgical treatment of chronic thromboembolic pulmonary hypertension

Chronic thromboembolic pulmonary hypertension has been classified in Group 4 of PH.[30] The incidence of CTEPH after acute PE is in the range of 0.5–2%. Prevalence of CTEPH in PE patients is 3.8%, as reported in the 2013 NICE guidelines.[175] Lifelong anticoagulation is recommended in all patients with CTEPH. Pulmonary endarterectomy is the treatment of choice for the disease. The operability of patients with CTEPH is determined by multiple factors that cannot easily be standardized; these are related to the suitability of the patient, the expertise of the surgical team, and available resources. Apart from major pulmonary vascular obstruction, the pathophysiology of CTEPH includes a pulmonary microvascular disease, which may be responsible for the poor outcome in some cases of PEA. Moreover, hypercoagulation, 'sticky' red blood cells, high platelet counts, and 'uncleavable' fibrinogen may further contribute to obliteration of the PAs in CTEPH. *In situ* PA thrombosis in patients who have CTEPH may also occur. Clinical symptoms and signs are non-specific or absent in early CTEPH, with signs of right HF only becoming evident in advanced disease. These subjects are the most difficult to treat.

Table 9 Recommendation for the use of graduated compression stockings

Graduated compression stockings (GCS) are effective in diminishing the risk of deep vein thrombosis (DVT) in hospitalized patients
In patients with proximal thrombosis, GCS (30 mmHg at the ankle) should be performed for at least 2 years after the acute event
Anti-embolism stockings cannot replace GCS during the day but must be applied during the night
DVT is associated with significant long-term complications such as the post-thrombotic syndrome. Preventive and therapeutic strategies (clinical scores and/or ultrasound evaluation) are needed for these patients

The indications for PEA in CTEPH patients is based on the following items:

- *Clinical*: patients with New York Heart Association Class II, III, and IV, independently from age.
- *Haemodynamic*: Precapillary PH, defined as a mPAP $\geq$ 25 mmHg with a PAWP $\leq$15 mmHg and a PVR $\geq$3 WU.
- *Anatomical*: surgical accessibility of thrombi in the main, lobar, or segmental PAs.[176] The expertise of the surgeon and of the Centre allows to treat lesions located not only in the main, lobar, and segmental but also in the subsegmental branches of PAs.[177]

Presence of severe pulmonary disease is an absolute contraindication to PEA.

Surgical technique

Surgical treatment has drastically changed in the last years.

From the beginning of the transplant programme for CTEPH, the attitude has changed from the lung–heart transplantation to the bipulmonar transplantation due to the RV inverse remodelling observed in the first patients. The extensive applicability of PEA in expert centres has allowed to reserve the potential lung donors to the treatment of pathology different from CTEPH. Many patients in previous observations who were judged inoperable for the clinical and anatomic conditions were successively treated with PEA with satisfactory long-term survival rates.[177–179]

The rationale of interventional treatment is the removal of all the chronic thromboembolic material from the pulmonary circulation, eliminating the cause for elevation of resistance. An important aspect of surgery is represented by the correct identification of the cleavage plane in the PA wall, or in the thickness of the tunica media, allowing the excision of the entire intima, in which the chronic thromboembolic are adherent. The myocardial protection is obtained, as well as with moderate hypothermia and intermittent reperfusion. During the entire procedure, cerebral oximetry is monitored using a near-infrared spectroscopy.

The modification of the San Diego Procedure allows a longer period of cardioplegia with a more accurate removal of thromboembolic material also in distal sites. Note that distal thrombi have a significant role in the haemodynamic function of the lung. However, in elderly subjects, long periods of cardioplegia in deep hypothermia are not recommended.[179]

Successful PEA is able to reduce pulmonary arterial haemodynamic with recovery of both cardiac and respiratory function and clinical benefit on exercise capacity and improving quality of life.[180,181]

Postoperative complications are rare, the most frequent are persistence of PH, right HF, airways bleeding, and pulmonary oedema after PEA reperfusion. In the long-term, however, recurrent PAH may occur. This event could be due to the onset of new embolic events (caused, for example, by poor management of anticoagulant therapy) or evidence of small vessel disease (*Eisenmenger similar*), especially in long-lasting CTEPH. This latter event is the reason why PEA is preferred when the patient is defined as NYHA Class II.

A pharmacological approach is recommended in symptomatic patients who have been classified as having inoperable CTEPH by a CTEPH team or in patients with very high surgical risk for severe co-morbidities.

Pharmacological treatment of chronic thromboembolic pulmonary hypertension

Although PEA is the treatment of choice for CTEPH,[30] 20–35% of patients have inoperable CTEPH (for anatomical reason, sites of thromboembolic material, and/or severe co-morbidities).[182] Despite the OAT, the mortality rate of these patients is 32% at 18 months, while long-term survival (5 years) is around 30%. This percentage dramatically decreases to 10% in patients with a PAP $>$ 50mmHg.[183,184]

Because not all patients are deemed operable and up to one-third have persistent or recurrent CTEPH after the procedure, several small, uncontrolled trials have investigated the response to drugs approved for PAH: endothelin receptor antagonists, prostacyclin analogues, and phosphodiesterase type 5 inhibitors in CTEPH.[185] The histopathologic pattern in these patients is analogous to the one of idiopathic PH.[186]

It seems that preoperative high levels of endothelin 1 correlate with the haemodynamic alterations observed in PEA and may be used to predict haemodynamic outcome after the interventional procedure.[187] These results are supported by other evidences that links PAH and CTEPH; for example, the nitric oxide (NO)–soluble guanylate cyclase (sGC)–cyclic guanosine monophosphate (cGMP) pathway in regulating pulmonary vascular tone is demonstrated by the dysregulation of NO production, sGC activity, and cGMP degradation in both PAH and CTEPH.[188]

Due to the lack of evidence in the treatment of CTEPH, in the past years, many drugs, in association with anticoagulant treatment, have been used off-label.[30] Unfortunately, this aspect has delayed the admission of

patients to CTEPH centres, in order to evaluate the role of PEA. San Diego Center performed a retrospective analysis of CTEPH patients referred for PAE during 2005–07. The authors observed that the number of patients already treated medically (off-label) was rising without a post-operative advantage.[189]

In 2008, the Bosentan Effects in iNonopErable Forms of chronIc Thromboembolic pulmonary hypertension (BENEFiT) study, a double-blind, randomized, placebo-controlled study in CTEPH included patients with either inoperable CTEPH or persistent/recurrent PH after PEA (>6 months after PEA). This study demonstrated a positive treatment effect of bosentan on haemodynamics in this patient population ($P < 0.0001$). However, no improvement was observed in exercise capacity and functional class.[190] As demonstrated by different authors, after PEA, long-term survival and cardiopulmonary function recovery is excellent in most patients but may need more than 2 years' time.[191] After the BENEFIT trial, Bosentan has not obtained the indication for medical treatment in inoperable or persistent CTEPH after PEA.

Riociguat is a member of a new class of therapeutic agents called sGC stimulators evaluated for its potential advantage over the other PAH treatments. In particular, Riociguat has a dual mode of action, directly stimulating sGC independently of NO and increasing the sensitivity of sGC to NO. Riociguat increases the level of cGMP, resulting in vasorelaxation and anti-proliferative and anti-fibrotic effects, as shown in experimental models of PH. The result should be an increase in the availability of NO, regardless of the endogenous initial levels with consequent vasodilatation, anti-fibrotic, anti-inflammatory, and anti-proliferative effect rather than a decrease in pulmonary vascular resistance.[192–194]

The PATENT PLUS trial evaluated the safety and efficacy of Riociguat in combination with Sildenafil in PAH patients. Patients receiving sildenafil (20 mg three times daily) were randomized to placebo or riociguat (up to 2.5 mg three times daily) for 12 weeks. This trial was stopped for the potentially unfavourable safety signals with sildenafil plus riociguat, possibly due to an important systemic vasodilation and symptomatic hypotension and no evidence of a positive benefit/risk ratio. Concomitant use of riociguat with phosphodiesterase 5 inhibitors is hence contraindicated.[189,195]

Riociguat was evaluated in the Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase-Stimulator Trial 1 (CHEST-1).[192] A total of 261 patients underwent randomization and received at least one dose of study medication (173 patients in the riociguat group and 88 in the placebo group).

Riociguat improved primary and secondary endpoints in both inoperable patients and patients with persistent/recurrent CTEPH vs. baseline, with a more marked effect in inoperable patients.[196] The drug has been well tolerated while most common side effects were related to vasodilation (headache and fatigue). The CHEST-2 open-label extension evaluated 237 patients (98% of patients enrolled in CHEST-1) in the long-term safety and efficacy of riociguat. The study showed that long-term riociguat had a favourable benefit–risk profile and apparently showed sustained benefits in exercise and functional capacity for up to 2 years. Side effects, such as haemoptysis, remains to be clarified.

Currently, a Phase II study with Macitentan (MERIT-1) is ongoing. This trial will evaluate the drug in both inoperable and recurrent CTEPH patients after PEA (main outcome will be a decrease in PVR).

In conclusion, the only drug therapy currently indicated in patients with inoperable, recurrent, or permanent CTEPH after PEA is riociguat. In particular, riociguat is recommended in symptomatic patients who have been classified as having inoperable CTEPH by a CTEPH team including at least one experienced PEA surgeon or have persistent/recurrent CTEPH after surgery. However, medical treatment before surgery in CTEPH patients is not able to modify the surgical outcome of these patients that should be referred to the expert centre for PEA as soon as possible, already in an NYHA functional Class II, not postponing a possible surgical correction.

Future trials must clarify some aspects such as the role of riociguat in long-term survival, and in combination therapy, and also the role of NOAs in CTEPH.

Special issues: clinical and outpatients management

The FU of the patient with VTE requires an appropriate medical service able to manage both the diagnostic and the therapeutic strategies of this complex disease. Indeed, it is essential that management of an outpatient VTE is based on a clinical care pathway that uses an integrated multidisciplinary approach able to provide a similar degree of effectiveness and safety as customary inpatient therapy.[197–199]

One of the main problems discussed in the last ESC guidelines on PE is the early discharge of low-risk patients.[2] However, these subjects have to be followed with the same attention and quality of cares that are offered to the hospitalized patients.[200]

Generally, after acute VTE, the patient is managed by his or her general practitioner (GP). This 'relationship' is based especially on the periodical anticoagulation management (VKA) and/or on the patient's revaluation that must be performed to assess the duration of anticoagulant treatment. Other specialists could be involved in this long-term management, such as cardiologists or internal medicine physicians, according to the patient's needs.

After analysing our manuscript and the current guidelines, there is a need to revise the current medical strategy in the FU of VTE, considering other models of care used in other cardiologic diseases.

Given the high incidence of VTE, high recurrent rates, several co-morbidities associated with the disease, the most appropriate health care system seems to be the creation of multidisciplinary teams that work in the same place.

Experienced physician and nurses must work together to obtain a higher standard of care.

This clinic must represent a simpler way to facilitate the patient–GP relationship.

Clinic's role should be:

- Monitoring of anticoagulation therapy: For this service a connection to the nearest laboratory is essential
- Periodical patient evaluation
- Routine laboratory evaluation
- Periodic clinical evaluation that must include:
  - electrocardiography
  - TTE
  - Vascular US
  - 6MWT
  - CPET
- Planning and interpretation of imaging tests:
  - CTA
  - LP scan
- Planning and evaluation of other tests that involve different aspects of medicine: cardiology, pulmonology, haematology, and internal medicine
- Planning and evaluation of additional tests (if not performed during the acute phase):
  - thrombophilia
  - unknown malignancies
- Planning change in anticoagulant therapy
- Planning anticoagulant withdrawal

The appropriate management for patients with complications must be also guarantee:

- Recurrent VTE that requires hospitalizations and/or therapeutic revaluation.
- Decisions regarding other treatment strategies in subjects with CTEPH should be made by a multidisciplinary team of experts and in collaboration with a surgical referee centre able to perform PEA.
- Bleeding events must be managed also with other specialists.

If surgical treatment could be performed in a hospital, this department must also realize protocols and audits with the aim of reducing VTE risk during hospitalization and managing new cases effectively.

Nurses must be an integral component of a CTEPH clinic. They should be able to record independently and follow various stages of the disease. In particular:

- examination planning;
- planning and first interpretation of laboratory tests;
- perform ultrasound vascular examination if trained;
- counselling for patients and their families;
- home monitoring and home nursing; and
- education and prevention of VTE.

The VTE clinic must create local 'diagnostic protocols' and therapeutic programmes, in accordance with the last scientific guidelines and the best clinical practice.

Medical staff should participate in the training and research projects in collaboration with other similar structures in order to increase their knowledge.

Future developments and conclusions

There is currently a lack of evidence regarding some aspects of VTE long-term management as optimal duration of anticoagulation in unprovoked VTE. There is a need for new markers able to indicate the treatment withdrawal when patients are at low risk for recurrent events. Moreover, it must be considered that also provoked VTE could be associated with other co-morbidities that could justify a longer anticoagulant treatment.

CTEPH patients must be followed in the long-term and also in this field other markers for the early detection of disease should be useful. Despite different studies have already assessed the role of NOACs in VTE, further investigation is needed, especially on the safety and efficacy in the long run. Furthermore, NOACS must also be investigated widely in cancer.

We hope that through the present manuscript, an increased attention will be given to the FU of VTE.

Appendix: algorithms

To perform an efficacious FU in patients with acute VTE, it is fundamental to perform a complete prognostic stratification during hospitalization because the short-term morbidity and mortality depends on this preliminary assessment. Assessment of haemodynamic stability at admission is fundamental for the early prognostic stratification. Indeed, the latter is the main discriminatory factor between high- and non-high-risk patients. PESI, Spesi, CTA, RVD, and clinical biomarkers allow to complete the prognostic assessment.[2] Co-morbidities, such as cancer or previous cerebrovascular disease, have an important role both in the short-term prognosis and in the treatment. Residual thrombosis in any sites (lung, RV, or peripheral veins) and/or RVD.

Despite in the past, it was thought that the only problem after discharge was the duration of anticoagulation we believe that nowadays FU must have the following objectives:

- assess the risk of recurrent VTE;
- assess the bleeding risk;
- define the duration and the type of anticoagulant therapy;
- assess the global cardiovascular risk; and
- identify patients with CTEPH.

To establish the risk of bleeding events during the 3 months, we recommend the use of the score adopted in RIETE registry.[14] Conversely, to assess the long-term bleeding risk, the CFCA should be applied.[9] Actually no scores have been proposed for NOACs. Bleeding risk is a fundamental part of the decision-making process.

Anticoagulant treatment after VTE is recommended for at least 3 months (active phase of treatment), followed by a second period (secondary prevention), which can vary with respect to the recurrence risk.

In general, morbidity and mortality in patients with VTE, especially in the mid-long-term period, is usually due to cancer and cardiovascular diseases. Special attention is requested with regard to these aspects.

CTEPH is a disease of obstructive PA remodelling as a consequence of major vessel thromboembolism. These patients must perform a TTE FU after 3 and 6 months, if in the acute phase they had RVD, PAP $>$50 mmHg, residual thrombosis, or dyspnoea.

Figure 1 is the suggested algorithm for FU in PE/VTE.

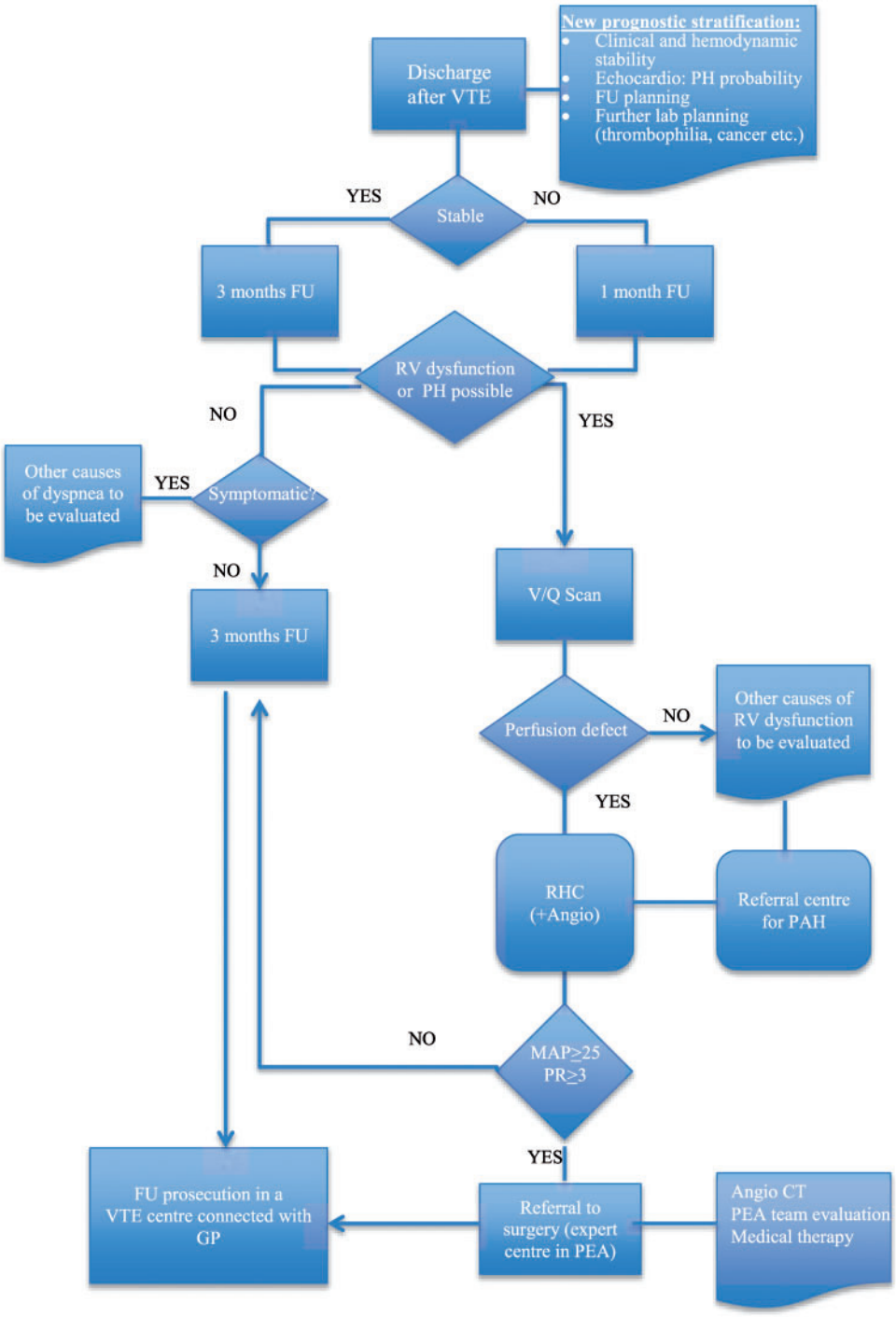

Figure 1 Decision algorithm for follow-up of venous thromboembolic patients. VTE, venous thromboembolism; PH, pulmonary hypertension; lab, laboratory; FU, follow up; RV, right ventricle; V/Q Scan, ventilation/perfusion scintigraphy; RHC, right heart catheterization; Angio, angiopneumography; PAH, pulmonary artery hypertension; MAP, pulmonary mean arterial pressure; PR, pulmonary resistance; GP: general practitioner; PEA, pulmonary endoarterectomy; Angio CT, computed angio tomography.

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