

# Residual Clot in Patients with Deep Vein Thrombosis and Pulmonary Embolism: Prognostic Implications

**Keywords:** Deep vein thrombosis; Pulmonary embolism; Venous thromboembolism; Post-thrombotic syndrome; Chronic thromboembolic pulmonary hypertension; Residual clot

## Abstract

In order to assess whether there is discordance in the timing of thrombus resolution between deep vein thrombosis (DVT) and pulmonary embolism (PE), we analyzed current evidence from recent major literature, and evaluated its prognostic implications. After an episode of proximal DVT, residual vein thrombosis (RVT), as shown with ultrasonography, is still detectable in approximately 50% of patients after three months, and in lower proportions afterwards. RVT is likely to represent a marker of hypercoagulability, and is associated with an approximately doubled risk for recurrent thromboembolism, post-thrombotic syndrome, arterial thrombotic events and cancer. Males, individuals with extensive thrombosis and those with previous thromboembolism have the highest likelihood of developing RVT. Conversely, based on recent findings in 85% of patients with PE a full recanalization, as shown by CT scanning, is achieved, and in the remaining patients the thrombotic mass decreases by 80%. No association exists between residual embolism and the risk for recurrent thromboembolism or chronic thromboembolic pulmonary hypertension. Accordingly, repeating CT scanning for prognostic implications does not seem justified. These findings add to the growing perception that DVT and PE are to be regarded as separate pathophysiological entities.

## Introduction

Although deep vein thrombosis (DVT) and pulmonary embolism (PE) are generally regarded as two clinical manifestations of the same disease, venous thromboembolism (VTE), and several elements induce to reconsider this assumption. For example, in up to 60% of patients with PE no clinical or objective manifestations of DVT are detectable [1-3]. The rate of recurrent VTE after discontinuation of anticoagulation is almost twice as high in patients with DVT as in those with PE [4]. In comparison with DVT patients, the risk of PE at recurrence is more than three times as high in patients with PE [5]. Finally, the rate of PE manifestations in patients with factor V Leiden is considerably lower than in non carriers, the so called "FVL paradox" [6,7].

In order to assess whether there is discordance in the timing of thrombus resolution between the two vascular disorders, we analyzed current evidence from recent major literature, and evaluated its prognostic implications.

## Residual Clot in Patients with DVT

According to findings of studies which used repeat ultrasound imaging, the thrombotic mass decreases over time in patients with proximal DVT [8,9]. However, residual vein thrombosis (RVT) is still



Paolo Prandoni\*

Department of Cardiovascular Sciences, University of Padua, Italy

\*Address for Correspondence:

Paolo Prandoni, Department of Cardiovascular Sciences, Thromboembolism Unit, University of Padua, Via Giustiniani 2, 35128, Padova, Italy, Tel: +39 049 8212656; Fax: +39 049 8218731; E-Mail: paoloprandoni@tin.it

Submission: 09 June, 2015

Accepted: 24 June, 2015

Published: 01 July, 2015

Reviewed & Approved by: Dr. Kerry Hitos, Executive Director, Department of Surgery, University of Sydney, Australia

detectable in approximately 50% of patients after three months, and in lower proportions afterwards [10]. Although the definition of RVT has varied according to the technique used for its detection, there is current agreement on the persistence of a thrombotic burden of at least 4 mm in diameter, as assessed with ultrasonography in the transverse section under maximum compressibility, in either the common femoral or the popliteal vein [11]. RVT is likely to represent a marker of hypercoagulability.

Whether RVT increases the risk of recurrent VTE is controversial, as there are data in favor and against this association [12-14]. In addition, whether RVT has the potential to predict the subsequent occurrence of other adverse events that are associated with hypercoagulability, such as the post-thrombotic syndrome (PTS), arterial thrombotic events and cancer is unknown.

In a recent prospective cohort study in a cohort of 869 patients with symptomatic proximal DVT, we related the development of recurrent VTE, PTS, symptomatic arterial thrombotic events and cancer to the presence of RVT at three months after the acute event. All patients received conventional anticoagulation [15]. The presence of RVT at 3 months after acute DVT was found in almost 50% of patients, and associated with an approximately doubled risk for recurrent VTE (hazard ratio [HR], 2.03; 95% CI, 1.40-2.94), PTS (HR, 2.34; 95% CI, 1.87-2.93), symptomatic arterial thrombotic events (HR, 2.05; 95% CI, 1.08-3.88) and cancer (HR, 3.09; 95% CI, 1.31-7.28). Males, individuals with extensive thrombosis and those with previous VTE were found to have the highest likelihood of developing RVT.

In this study, however, the impact of competing risks could only be partially obviated. In addition, all events were included in the analysis whichever their severity. Therefore, we performed a subsequent analysis, in which we regarded objectively proven recurrent VTE, severe PTS, manifest cancer, acute myocardial infarction or paralyzing stroke as having comparable high-degree severity, and pointed at the cumulative incidence of this combined end-point [16]. Once again, serious complications developed in more than twice as many patients with than without RVT (HR, 2.51; 95% CI, 1.87 to 3.36).

While the association with the risk of recurrent VTE is consistent with the results of a recent patient-level meta-analysis of most available investigations addressing this issue [13], the definitely increased risk of PTS, arterial thrombotic events and cancer was an unexpected finding. For the long-term clinical management of patients with proximal DVT a single assessment of RVT has, therefore, the potential to guide treatment decisions by enabling a better risk-stratification of patients. Based on these findings, RVT is likely to be by far the most important single predictor of PTS development. Of interest, in a subsequent analysis conducted in 1081 cancer-free patients with DVT the presence of RVT was found to be an independent predictor of subsequent overt malignancy in the only subgroup of patients with unprovoked DVT [17].

If RVT may help identify individuals in whom anticoagulant therapy can be safely discontinued after an episode of DVT is uncertain. In 2009, we published the results of a randomized clinical trial, in which 538 patients with acute proximal DVT who had completed an uneventful 3-month period of anticoagulation were randomized to a fixed duration of anticoagulation (i.e., no further anticoagulation for secondary thrombosis, an extra 3-month for unprovoked thrombosis) or to a flexible duration of ultrasound-guided anticoagulation (i.e., no further anticoagulation in patients with recanalized veins, continuation of anticoagulation in all other patients up to a maximum of 9 months for secondary and 21 months for unprovoked thrombosis) [18]. Recurrent VTE developed in 46 (17.2%) of the 268 patients allocated to the fixed anticoagulant duration and in 32 (11.9%) of the 270 randomized to the flexible duration, for an adjusted hazard ratio (HR) of 0.64 (95% CI, 0.39 to 0.99).

Tailoring the duration of anticoagulation based on ultrasound findings is, therefore, likely to reduce the rate of recurrent VTE in patients with proximal DVT. However, the rate of recurrent VTE in those with earlier vein recanalization was not reassuringly low. In this regard, the results of the recently published DULCIS study appear of particular interest [11]. The adoption of an algorithm incorporating both RVT and serial D-Dimer was found to identify a substantial proportion of patients with unprovoked DVT in who anticoagulation can be safely discontinued (annual rate of recurrent VTE, 3.0%). According to recent findings, RVT can be of help for predicting the risk of recurrent VTE also in patients with cancer [19].

### Residual Clot in Patients with PE

The rate of residual thrombosis, defined as the long-term persistence of thrombotic material in the pulmonary artery tree following pulmonary embolism (PE), is uncertain. Although a recent systematic review reported low rates of recanalization (43% at 6 months) [20], most studies used suboptimal methods for detection, such as perfusion lung scanning or older generation computed tomography (CT) scanners.

In a multicenter prospective study we determined the rate of residual thrombosis in a cohort of 113 consecutive patients with acute PE, as detected by 64-row multi detector CT, who were treated with anticoagulants alone and were re-assessed six months later with the same high-technology procedure [21]. The degree of artery obstruction (CT index) at baseline and after six months was calculated with the Qanadli scoring system [22]. Of these patients, 96 (85.0%) achieved

full recanalization, while in the remaining 17 the CT index decreased from 50.0% to 5.6%. In only one patient was an intraluminal filling defect seen, while in the remaining the most common patterns were eccentric defects, vessel narrowing or occlusion, bands and webs, and post-stenotic dilatation. Male gender and the severity of pulmonary obstruction were independently associated with the occurrence of residual thrombosis.

Our findings are consistent with those of a similar observation conducted in the Netherlands [23]. In this study, 157 consecutive patients with acute PE diagnosed by multi detector CT underwent follow-up imaging with the use of the same technology after six months of anticoagulant treatment, and were then followed-up for 2.5 years. At baseline, the median obstruction index was 27.5%. After six months of treatment, complete PE resolution occurred in 82 patients (84.1%). The median obstruction index of the 25 patients with residual thrombotic obstruction was 5.0%. During follow-up, 16 patients (10.2%) experienced recurrent VTE. The presence of residual thromboembolic obstruction was not associated with recurrent VTE (adjusted HR, 0.92; 95% CI: 0.2 to 4.1).

These findings, combined with the absence of a correlation between residual thrombotic obstruction and recurrent VTE, do not support the routine use of follow-up CT imaging in patients treated for acute PE. In addition, they most likely account for the low risk of chronic thromboembolic pulmonary hypertension [24], which contrasts with the high rate of PTS complications following an episode of DVT [15]. Finally, as for the time being detection of small and unspecific residual defects is unlikely to have any appreciable relevance in the management of patients with PE, repeating CT scanning for prognostic implications does not seem justified.

### Conclusions

Timing and modalities of clot resolution in patients with DVT differ remarkably from those of patients with PE, as do their prognostic implications. Our findings, together with those coming from other centers, add to the growing perception that, although DVT and PE share many similarities, they are likely to be regarded as separate pathophysiological entities.

### References

1. Hull RD, Hirsh J, Carter CJ, Jay RM, Dodd PE, et al. (1983) Pulmonary angiography, ventilation lung scanning and venography for clinically suspected pulmonary embolism with abnormal perfusion lung scan. *Ann Intern Med* 98: 891-899.
2. Giuntini C, Di Ricco G, Marini C, Melillo E, Palla A (1995) Epidemiology. *Chest J* 107: 3S-9S.
3. Goldhaber SZ, Grodstein F, Stampfer MJ, Manson JE, Colditz GA, et al. (1997) A prospective study of risk factors for pulmonary embolism in women. *JAMA* 277: 642-645.
4. Kovacs MJ, Kahn SR, Wells PS, Anderson DA, Chagnon I, et al. (2010) Patients with a first symptomatic unprovoked deep vein thrombosis are at higher risk of recurrent venous thromboembolism than patients with a first unprovoked pulmonary embolism. *J Thromb Haemost* 8: 1926-1932.
5. Baglin T, Douketis J, Tosetto A, Marcucci M, Cushman M, et al. (2010) Does the clinical presentation and extent of venous thrombosis predict likelihood and type of recurrence? A patient-level meta-analysis. *J Thromb Haemost* 8: 2436-2442.
6. Desmarais S, de Moerloose P, Reber G, Minazio P, Bounameaux H, et al. (1996) Resistance to activated protein C in an unselected population of patients with pulmonary embolism. *Lancet* 347: 1374-1375.

7. Martinelli I, Cattaneo M, Panzeri D, Mannucci PM (1997) Low prevalence of factor V: Q506 in 41 patients with isolated pulmonary embolism. *Thromb Haemost* 77: 440-443.
8. Prandoni P, Cogo A, Bernardi E, Villalta S, Polistena P, et al. (1993) A simple ultrasound approach for detection of recurrent proximal-vein thrombosis. *Circulation* 88: 1730-1735.
9. van Ramshorst B, van Bemmelen PS, Hoeneveld H, Faber JA, Eikelboom BC (1992) Thrombus regression in deep venous thrombosis. Quantification of spontaneous thrombolysis with duplex scanning. *Circulation* 86: 414-419.
10. Prandoni P, Lensing AW, Prins MH, Bernardi E, Marchiori A, et al. (2002) Residual venous thrombosis as a predictive factor of recurrent venous thromboembolism. *Ann Intern Med* 137: 955-960.
11. Palareti G, Cosmi B, Legnani C, Antonucci E, De Micheli V, et al. (2014) D-dimer to guide the duration of anticoagulation in patients with venous thromboembolism: a management study. *Blood* 124: 196-203.
12. Tan M, Mos IC, Klok FA, Huisman MV (2011) Residual venous thrombosis as predictive factor for recurrent venous thromboembolism in patients with proximal deep vein thrombosis: a systematic review. *Br J Haematol* 153: 168-178.
13. Donadini MP, Ageno W, Antonucci E, Cosmi B, Kovacs MJ, et al. (2014) Prognostic significance of residual venous obstruction in patients with treated unprovoked deep vein thrombosis: a patient-level meta-analysis. *Thromb Haemost* 111: 172-179.
14. Carrier M, Rodger MA, Wells PS, Righini M, LE Gal G (2011) Residual vein obstruction to predict the risk of recurrent venous thromboembolism in patients with deep vein thrombosis: a systematic review and meta-analysis. *J Thromb Haemost* 9: 1119-1125.
15. Prandoni P, Lensing AW, Prins MH, Pesavento R, Piccioli A, et al. (2015) The impact of residual thrombosis on the long-term outcome of patients with deep venous thrombosis treated with conventional anticoagulation. *Semin Thromb Hemost* 41: 133-140.
16. Prandoni P, Lensing AW, Prins MH, Villalta S, Harenberg J, et al. (2015) Residual vein thrombosis and the risk of subsequent serious complications. *Thromb Res* 136: 178-179.
17. Prandoni P, Lensing AW, Prins MH, Negri S, Villalta S, et al. (2015) Venous thrombotic burden and the risk of subsequent overt cancer. *Thromb Haemost* [Unpublished data].
18. Prandoni P, Prins MH, Lensing AW, Ghirarduzzi A, Ageno W, et al. (2009) Residual thrombosis on ultrasonography to guide the duration of anticoagulation in patients with deep venous thrombosis: a randomized trial. *Ann Intern Med* 150: 577-585.
19. Napolitano M, Saccullo G, Malato A, Sprini D, Ageno W, et al. (2014) Optimal duration of low molecular weight heparin for the treatment of cancer-related deep vein thrombosis: the Cancer-DACUS Study. *J Clin Oncol* 32: 3607-3612.
20. Nijkeuter M, Hovens MM, Davidson BL, Huisman MV (2006) Resolution of thromboemboli in patients with acute pulmonary embolism: a systematic review. *Chest* 129: 192-197.
21. Pesavento R, Filippi L, Pagnan A, Visonà A, Pauletto P, et al. (2014) Unexpectedly high recanalization rate in patients with pulmonary embolism treated with anticoagulants alone. *Am J Respir Crit Care Med* 189: 1277-1279.
22. Qanadli SD, El Hajjam M, Vieillard-Baron A, Joseph T, Mesurolle B, et al. (2001) New CT index to quantify arterial obstruction in pulmonary embolism: comparison with angiographic index and echocardiography. *Am J Roentgenol* 176: 1415-1420.
23. den Exter PL, van Es J, Kroft LJ, Erkens PM, Douma RA, et al. (2015) Thromboembolic resolution assessed by CT pulmonary angiography after treatment for acute pulmonary embolism. *Thromb Haemost* 114 [Epub ahead of print].
24. Pengo V, Lensing AW, Prins MH, Marchiori A, Davidson BL, et al. (2004) Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. *N Engl J Med* 350: 2257-2264.