

Deep Vein Thrombosis in Emergency Department: A Simplified Systematic Approach

Cinzia Nitti, Francesca Riccomi, Lucia Salvi, Susanna Contucci and Aldo Salvi*

Department of Emergency, Ospedali Riuniti Ancona, Torrette Ancona, Italy

Abstract

Management of patients with Deep Vein Thrombosis (DVT) in the Emergency Department (ED) has dramatically changed over the last 10 years in the absence of a shared management, leading to the need of a shared consensus strategy to standardize the diagnostic and therapeutic approach in acute phase of DVT in a setting where standardization is particularly difficult due to the volume of activity and the number of operators who alternate in the care of the individual patient. We perform a review and comment of a NGT work performed by a panel of 5 Italian experts who developed 21 consensus statements based on available evidence and their clinical experience. Considering the best available evidence and the longstanding clinical experience of 5 Italian EDs' experts, the management of patients with suspected DVT to ED should be characterized by a standardized diagnostic process, guided by the estimation of pre-test clinical probability with formal and validated Clinical Prediction Rule (CPR), an increase in the number of patients discharged directly from the ED, reserving hospitalization only for high-risk patients and faster and more appropriate use of the wide range of anticoagulant drugs currently available. In conclusion such a guide will standardize the diagnostic and therapeutic approach in acute phase of DVT, limit the number of diagnostic tests performed to exclude or confirm DVT and shorten the stay time of these patients in ED without reducing safety. Indeed, the identification of simple criteria for the definition of high-risk DVT together with availability of DOACs will allow physicians to safely discharge all DVT patients who do not meet these risk criteria, directly from the emergency room.

Keywords: Deep vein thrombosis • Diagnosis • Risk stratification • Anticoagulant drugs • Critical care • Emergency department

Abbreviations: DVT: Deep Vein Thrombosis; ED: Emergency Department; CPR: Clinical Prediction Rule; CUS: Compression Ultrasound Sonography; LMWH: Low-Molecular Weight Heparin; UFH: Unfractionated Heparin; DOACs: Direct Oral Anticoagulants

Introduction

Management of patients with Deep Vein Thrombosis (DVT) has dramatically but not homogeneously changed over the last 10 years. PREFER in VTE registry, a real-life study that evaluated the management of patients with venous thromboembolism in Europe, showed that Italian patients receive heparin as initial treatment more frequently and are more often hospitalized than those of other European countries: 65.4% of these refer to the Emergency Department (ED) [1]. Therefore, the need to standardize behaviors resulted in the development of such a consensus document. In this work, a panel of 5 Italian experts developed 21 consensus statements based on available evidence and their clinical experience [2].

Literature Review

For DVT diagnostic process in the ED the study group emphasizes the central role of three elements

Assessment of the pretest probability: There are several formal risk models available to assess the pre-test probability of DVT. The two-level Wells Score is the most widely used and is recommended by the panel, even if not easily memorable (Table 1) [3,4].

According to this model, DVT is likely if the score is ≥ 2 (prevalence 28%) and unlikely if score < 2 (prevalence 8%).

D-dimer test: It is a sensitive but non-Specific measure of thrombosis, indeed D-dimer is not only elevated in patients with DVT but also in a variety of other common conditions including, but not limited to, inflammatory diseases,

***Address for Correspondence:** Aldo Salvi, Department of Emergency, Ospedali Riuniti Ancona, Torrette Ancona, Italy; Tel: 0039 (0)71 596 4027; E-mail: aldo.salvi@ospedaliriuniti.marche.it

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malignancy, pregnancy, surgery, trauma, and advanced age. This makes the test useful to rule out DVT when negative, but has no diagnostic value when positive. In the ED, the panel recommends the use age adjusted cut-off d-dimer as follow: up to 50 years cut-off 500 ng/ml, above 50 years cut-off age $\times 10$ [5]. In all studies the use of age-adjusted D-Dimer cut-offs reduced unnecessary investigations without reducing safety [6], but although in a recent observational study some authors question these advantages, they are not easily comparable with other studies due to the different threshold of negativity of tests available (250 ng/ml) [6].

Therefore it is defined that the combination of an "unlikely" Wells score and a negative age-adjusted D-dimer excludes DVT in both outpatients and inpatients of both sexes with a 1.2% failure rate (95% CI: 0.7% to 1.8%) considerably reducing unnecessary investigations: but the d-dimer determination is underutilized in this setting [7]. Instead the panel highlights an alert: in patients with cancer or with previous DVT the original Wells rule is less safe, in fact Geersing, et al.[4] in these subgroups observed a failure rate $> 2\%$, a threshold universally considered not to be exceeded [8].

Leg venous Compression Ultrasound Sonography (CUS): Even though complete or whole-leg duplex venous ultrasound (VDUS) remains the gold-standard test for the diagnosis of DVT, for the ED setting the panel

Table 1. Wells clinical model to predict pretest probability of DVT.

Clinical findings	Points
Paralysis, paresis or recent orthopedic casting of lower extremity	1
Bedridden > 3 days recently or major surgery within past 12 weeks	1
Localized tenderness of the deep veins	1
Swelling of entire leg	1
Calf swelling 3 cm greater than other leg (measured 10 cm below tibial tuberosity)	1
Non-varicose collateral superficial veins	1
Active cancer or cancer treated within 6 months	1
Previously documented DVT	1
Alternative diagnosis at least as likely as DVT (Baker's cyst, cellulitis, muscle damage, superficial vein thrombosis, post-thrombotic syndrome, inguinal lymphadenopathy, extrinsic venous compression)	-2

encourages the use of CUS, both “2 points” (also called “limited”, which investigate the popliteal and common femoral veins) and “3 points” (also called “extended”, which investigate the popliteal veins, common femoral and superficial femoral veins). This represents a simple and extremely accurate non-invasive point-of-care test for the diagnosis of DVT, and can be easily performed in the ED by a trained emergency physician [9,10]. The method has been reviewed and defined in detail in a recent multidisciplinary consensus, very useful for the emergency setting [11]. In doubtful cases, when a complete venous evaluation is not available or difficult to perform in a reasonable time, the panel suggests to repeat a second CUS at 5-7 days but to undertake anticoagulant therapy if the patient’s bleeding risk is not excessive [12]. In this case the risk of thrombosis extension should be considered in order to decide whether to start anticoagulation or not. Risk factors for DVT extension are positive D-dimer test, severe symptoms, extended thrombosis (>5 cm in length, >7 mm in diameter or involving multiple veins), thrombosis localized near a proximal circulation vein, absence of removable risk factors, history of previous DVT or active cancer and in-patients status [13].

Suggested diagnostic pathways are summarized in Figure 1.

As for pregnant patients, neither D-dimer alone nor clinical prediction rules should be used to rule out VTE, in such setting the panel suggest the LEFT score replaces the Wells score: it attributes one point in the case of left (“L”) leg suspicion, one point for edema (“E”) and one point if the suspicion occurred during the first trimester (“F”) of pregnancy. The DVT probability is “unlikely” with score 0 (risk of DVT 0%) and “likely” with score ≥ 1 (risk of DVT 11.7%) [14]. The panel agrees that in absence of specific symptoms, further investigations for the diagnosis of PE are not necessary, as no short- or long-term clinical or therapeutic consequences were expected. Such a consideration is according to results derived from a cohort of 103 patients with deep vein thrombosis of lower limbs in which the prevalence of asymptomatic PE was 66% and no significant recurrence rate of thrombotic events was observed in the asymptomatic PE group during the follow-up [15].

As for DVT treatment in the acute phase, experts suggest to evaluate bleeding risk before the initiation of anticoagulant therapy using VTE BLEED risk score [16], a specific and validated risk score which must be rapid and easy to use in the ED (Table 2).

Anticoagulant therapy represents the mainstay of medical therapy for DVT. Treatment may include subcutaneous, weight adjusted Low-Molecular Weight Heparin (LMWH), fondaparinux, unfractionated heparin (UFH) and direct oral anticoagulants (DOACs). In acute phase the panel believes useful to make the following recommendations.

- In case of obesity and renal failure, unfractionated heparin continuous intravenous infusion or subcutaneous injections represents the treatment of choice [17].
- In case of pregnancy, treatment of choice is currently LMWH [18].
- In all other situations, DOACs should be considered as the first line anticoagulant therapy in non-cancer patients with DVT [19], and, in detail, if Apixaban and Rivaroxaban have evidence of efficacy and safety as single drug approach, initiated immediately on ED, Dabigatran and Edoxaban require pre-treatment with LMWH or fondaparinux for 5-7 days.
- Edoxaban, Rivaroxaban and, recently, Apixaban should be considered a valid alternative to LMWH also for the management of cancer related DVT, considering the increased risk of bleeding in patients with gastrointestinal cancer [20].
- DOACs must be avoided in patient suffering from severe renal failure, moderate to severe liver disease, antiphospholipidic syndrome, DVT in atypical districts, and maybe in patients with vena cava filters [21].

Regarding DVT management consensus statement, experts recommend strongly out of hospital management according to most recent guidelines [22], with acknowledging the following exceptions

- Ongoing bleeding or high bleeding risk (VTE BLEED risk score)
- Severe renal failure (eVFG <30 ml/min)
- Metastatic cancer
- Massive DVT, involving iliac femoral vein, caval vein or severely symptomatic patients (phlegmasia dolens)
- Inadequate home-care setting.

Data derived from Lozano [23] revealed that patients treated as outpatient

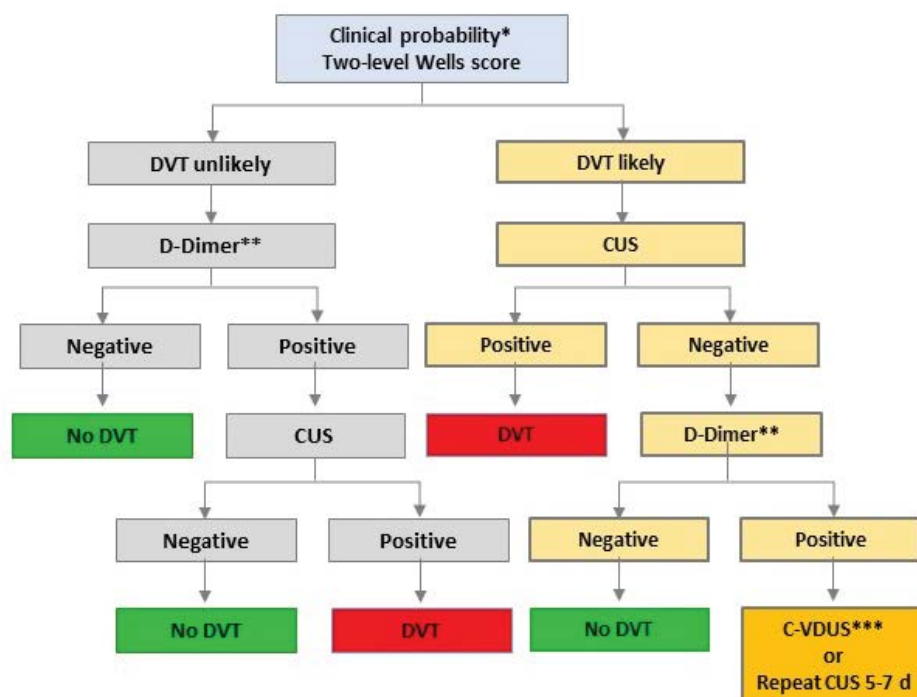


Figure 1. Suggested diagnostic pathways. *Clinical probability can be assessed by Wells score instead of experienced clinician gestalt. **D-dimer should be measured using a highly sensitive assay to rule out DVT; ***C-VDUS=complete venous duplex ultrasound.

Table 2.The VTE Bleed score: <2 Low bleeding risk; = 2 High bleeding risk.

Clinical findings	Points
Active cancer	2
Male patients with uncontrolled hypertension SBP >140 mmHg)	1
Anaemia (Ubc<13,0 g/dl men; Hbc<12,0 g/dl women)	1,5
History of bleeding (major or non-major clinically relevant bleeding)	1,5
Renal dysfunction (Cr Cl 30-60 ml/min)	1,5
Age>60 years	1,5

have an equal recurrence rate of venous thromboembolic events and lower rate of major bleeding than those managed as inpatient. Similarly, a Cochrane review [24] suggests that patients treated at home with Low Molecular Weight Heparin (LMWH) are less likely to have recurrence of VTE with no clear differences both in major or minor bleeding and in mortality than those treated as inpatients.

Discussion

Why is this paper important and what does this paper add compared to previous evidence?

This paper represent a simple and concise guidance on the management of DVT in the EDs: From the early diagnosis to risk stratification, initial treatment and early discharge, based upon the best available information, including situations where the actual evidences are limited.

Indeed, although several diagnostic algorithms have been developed and international guidelines encourage early discharge of low risk DVT patients, there are no clear indications for the diagnostic strategy and the subsequent management of DVT in the ED, leading to an extreme variability in management of DVT patient between emergency physicians. Consider this; a structured consensus technique appears a well-suited method to develop practical recommendations in this setting.

How is this paper likely to change practice?

The NGT study provides clear, unique and concise information on the management of DVT patients at the ED, based on the best available evidence and on the longstanding clinical experience of 5 Italian EDs' experts.

In the management of patients with suspected DVT to ED, we expect

1. A more standardized diagnostic process, guided by the estimation of pre-test clinical probability with formal and validated Clinical Prediction Rule (CPR) this will allow clinicians to select patients to refer to II level investigations, limiting the number of diagnostic tests performed to exclude or confirm DVT without reducing its safety.
2. A significant reduction in the stay time of these patients in ED, helping to reduce overcrowding.
3. An increase in the number of patients discharged directly from the ED, reserving hospitalization only for high-risk patients, leading to patient satisfaction and lower healthcare costs. Indeed, the identification of precise criteria for the definition of high-risk DVT together with availability of DOACs will allow physicians to safely discharge all DVT patients who do not meet these risk criteria, directly from the emergency room.
4. Faster and more appropriate use of the wide range of anticoagulant drugs currently available, personalizing the choice and above all increasing the proportion of patients discharged from ED with a single drug approach DOAC.

Conclusion

In summary such a guide will standardize the diagnostic and therapeutic approach in acute phase of DVT in a setting where standardization is particularly difficult, due to the volume of activity and the number of operators who alternate in the care of the individual patient.

Conflict of Interest

No conflict of interest related to this article.

References

1. Francesco, Guercini, Mommi Valeria, Camporese Giuseppe and Tonello Chiara, et al. "The Management of Patients with Venous Thromboembolism in Italy: Insights from the PREFER in VTE Registry." *Intern Emerg Med* 11 (2016):1095-1102.
2. Aldo, Salvi, Nitti Ciniza, Fabbri Andrea and Groff Paolo, et al. "Diagnosis and Treatment of Deep Vein Thrombosis in the Emergency Department: Results of an Italian Nominal Group Technique Study." *Clin Appl Thromb Hemost* 26 (2020).
3. Philip S, Wells, Anderson David R, Rodger Marc and Forgie Melissa, et al. "Evaluation of D-dimer in the Diagnosis of Suspected Deep-Vein Thrombosis." *N Engl J Med* 13 (2003):1227-1235.
4. Geersing GJ, Zuihoff NPA, Kearon C and Anderson DR, et al. "Exclusion of Deep Vein Thrombosis Using the Wells Rule in Clinically Important Subgroups: Individual Patient Data Meta-Analysis." *BMJ* 348 (2014): 1340.
5. Peter M, Reardon, Patrick Sean, Taljaard Monica and Thavorn Kednapa, et al. "Diagnostic Accuracy and Financial Implications of Age-Adjusted D-Dimer Strategies for the Diagnosis of Deep Venous Thrombosis in the Emergency Department." *J Emerg Med* 56 (2019): 469-477.
6. Mads, Nybo and Hvas Anne-Mette. "Age-Adjusted D-dimer cut-off in the Diagnostic Strategy for Deep Vein Thrombosis: A Systematic Review." *Scand J Clin Lab Invest* 77 (2017):568-573.
7. Mousa, Albeir Y, Mike Broce, David De Wit and Mina Baskharoun "Appropriate Use of Venous Imaging and Analysis of the D-Dimer/Clinical Probability Testing Paradigm in the Diagnosis and Location of Deep Venous Thrombosis." *Ann Vasc Surg* 50 (2018): 21-29.
8. CEA, Dronkers, van der Hulle T, Le Gal G and Kyrle PA, et al. "Subcommittee on Predictive and Diagnostic Variables in Thrombotic Disease. Towards a Tailored Diagnostic Standard for Future Diagnostic Studies in Pulmonary Embolism: Communication from the SSC of the ISTH." *J Thromb Haemost* 15 (2017):1040-1043.
9. Fulvio, Pomerio, Dentali Francisco, Borretta Valentina and Bonzini Matteo, et al. "Accuracy of Emergency Physician-Performed Ultrasonography in the Diagnosis of Deep-Vein Thrombosis: A Systematic Review and Meta-Analysis." *Thromb Haemost* 109 (2013):137-145.
10. Dehbozorgi, Afsaneh, Fatemeh Damghani, Razieh Sadat Mousavi-Roknabadi and Mehrdad Sharifi, et al. "Accuracy of Three-Point Compression Ultrasound for the Diagnosis of Proximal Deep-Vein Thrombosis in Emergency Department." *J Res Med Sci* 24 (2019): 80.
11. Laurance, Needleman, Cronan John J, Lilly Michael P and Merli Geno J, et al. "Ultrasound for Lower Extremity Deep Venous Thrombosis: Multidisciplinary Recommendations from the Society of Radiologists in Ultrasound Consensus Conference." *Circulation* 137 (2018): 1505-1515.
12. Johnson, Stacy A, Scott M Stevens, Scott C Woller and Erica Lake, et al. "Risk of Deep Vein Thrombosis following a Single Negative Whole-Leg Compression Ultrasound: A Systematic Review and Meta-Analysis." *Jama* 303 (2010): 438-45.
13. Shunichiro, Fujioka, Ohkubo Hiroto, Kitamura Tadashi and Mishima Toshiaki, et al. "Risk Factors for Progression of Distal Deep Vein Thrombosis." *Circ J* 84 (2020):1862-1865.
14. Chan, Wee-Shian, Agnes Lee, Frederick A Spencer and Mark Crowther, et al. "Predicting Deep Venous Thrombosis in Pregnancy: Out in "LEFT" Field?" *Ann Intern Med* 151 (2009): 85-92.

15. Mariea Jose, García-Fuster, Fabia Mariea Jose, Furió Elena and Pichler Gernot, et al. "Should we Look for Silent Pulmonary Embolism in Patients with Deep Venous Thrombosis?" *BMC Cardiovasc Disord* 14 (2014): 1-5.
16. Yuji, Nishimoto, Yamashita Yugo, Morimoto Takeshi and Saga Syunsuke, et al. "Validation of the VTE-BLEED Score's Long-Term Performance for Major Bleeding in Patients with Venous Thromboembolisms: From the COMMAND VTE Registry." *J Thromb Haemost* 18 (2020): 624-632.
17. Edith A, Nutescu, Spinler Sarah A, Wittkowsky Anna and Dager William, et al. "Low-Molecular-Weight Heparins in Renal Impairment and Obesity: Available Evidence and Clinical Practice Recommendations across Medical and Surgical Settings." *Ann Pharmacother* 43 (2009): 1064-1083.
18. Ariel, Many and Koren Gideon. "Low-Molecular-Weight Heparins during Pregnancy." *Can Fam Physician* 51 (2005): 199-201.
19. VS, Bedi, Grover Tarun, Sekhar R and Sekar N. "Consensus Document on Anticoagulant Management of Deep Vein Thrombosis: A Review." *Indian J Vasc Endovasc Surg* 8 (2021): 5-10.
20. Casey, O'Connell, Escalante Carmen P, Goldhaber Samuel Z and Mc Bane Robert, et al. "Treatment of Cancer-Associated Venous Thromboembolism with Low-Molecular-Weight Heparin or Direct Oral Anticoagulants: Patient Selection, Controversies, and Caveats." *Oncologist* 26 (2021): e8-e16.
21. Lucia, Mazzolai, Aboyans Victor, Ageno Walter and Agnelli Giancarlo, et al. "Diagnosis and Management of Acute Deep Vein Thrombosis: A Joint Consensus Document from the European Society of Cardiology Working Groups of Aorta and Peripheral Vascular Diseases and Pulmonary Circulation and Right Ventricular Function." *Eur Heart J* 39 (2018): 4208-4218.
22. Thomas L, Ortel, Neumann Ignacio, Ageno Walter and Beyth Rebecca, et al. "American Society of Hematology 2020 Guidelines for Management of Venous Thromboembolism: Treatment of Deep Vein Thrombosis and Pulmonary Embolism." *Blood Adv* 4 (2020): 4693-4738.
23. Francisco, Lozano, Trujillo-Santos Javier, Barrón Manuel and Gallego Pedro, et al. "Home Versus in-Hospital Treatment of Outpatients with Acute Deep Venous Thrombosis of the Lower Limbs." *J Vasc Surg* 59 (2014):1362-1367.
24. Richard, Othieno, Abu Affan Mayada and Okpo Emmanuel. "Home Versus in-patient Treatment for Deep Vein Thrombosis." *Cochrane Database Syst Rev* 18 (2018).

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