Editorial

Do isolated calf deep vein thrombosis need anticoagulant treatment?

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Isolated calf deep vein thrombosis (ICDVT), defined as thrombosis confined to the infra-popliteal veins of the lower limbs, is a frequent finding in symptomatic out- and in-patients when the ultrasound examination is extended to the whole deep leg veins. Studies based on a complete investigation of deep veins in the whole leg, reported a prevalence of ICDVT of 7–11% in cases with suspected PE, 4–15% in cases with suspected DVT, and 23–59% in patients with diagnosis of DVT (1). Notwithstanding these high figures, many and clinically relevant aspects of ICDVT are still controversial; in fact, that of ICDVT is currently one of the most debated issues in the field of venous thromboembolism (VTE). First of all, whether an extended ultrasound examination of calf deep veins is necessary in all suspected subjects is still matter of discussion and the American College of Chest Physician guidelines on VTE in the last edition (2) propose a rationale for not routinely examining the distal veins, based on the facts that: (I) other assessment (e.g., low clinical probability and/or negative D-dimer) may help guiding those in whom distal examination is not necessary; (II) a repeat ultrasound of the proximal veins can be done after a week to identify those patients with a risky proximal DVT; and finally, (III) false-positive findings for DVT may occur with a subsequent unnecessary and risky anticoagulant treatment to a number of subjects. Moreover, even in the case that the calf veins are imaged and ICDVTs are diagnosed, the above mentioned guidelines suggest two different management options as equally suitable in clinical practice: (I) to treat patients with anticoagulant therapy; or (II) to not treat patients with anticoagulant therapy unless extension of their DVT is detected on a follow-up ultrasound examination (e.g., after 1 or 2 weeks). However, important differences on this issue are present among currently available international guidelines on VTE; these differences reflect the broad variability in clinical practice between the strategies on how to manage patients with suspected leg DVT and even on how to treat ICDVT after diagnosis. The treatment for ICDVT is even not mentioned at all by the National Clinical Guideline Centre (last published in June 2012) since the guideline "*…focused on proximal DVT rather than isolated calf vein DVT as the latter is less likely to cause post-thrombotic syndrome than proximal DVT and also less likely to embolize to the lungs*." (3). In contrast, the International Consensus Statement on prevention and treatment of VTE affirms that evidence "*…indicates that oral anticoagulants should be given to all patients with symptomatic isolated calf DVT and that three months seems to be sufficient*." (4). It is really evident that the diagnostic and therapeutic approaches to suspected or diagnosed ICDVT vary greatly among guidelines as well as among even expert professionals and in clinical practice. This seems mainly attributable to the fact that the natural history of calf-limited DVTs, their potential risk and optimal treatment have, to date, not been sufficiently investigated. Thus, different options and clinical decisions are possible and equally justified. Evidence on the natural history of ICDVT is currently insufficient especially because in most studies ICDVTs, once diagnosed were treated with anticoagulants and, therefore, their natural history was modified by the treatment. Evidence on clinical evolution of diagnosed ICDVT left untreated is scarce. The proximal extension rate of untreated ICDVT

was reported to range between 10% and 15% in recent reviews (5,6). The CALTHRO study showed that 90% of untreated ICDVTs, diagnosed in patients well monitored with serial CUS, did not reach the proximal veins and/or embolize; the proximal extension rate at 7 days after diagnosis was as low as about 3% (7), in line with results (1–5.7%) of studies based on serial proximal ultrasound evaluations (8). These data support the view that the need of anticoagulant treatment in all patients with ICDVT has not been proved for sure. At last, one randomized, placebo controlled, clinical trial on the need of anticoagulation in patients with ICDVT has recently been published (9). The CACTUS study randomized patients with a first ICDVT to receive therapeutic nadroparin dose (170 UI/kg) or placebo for 42 days. There was no significant difference between the groups in the composite primary outcome: 3% in the nadroparin group and 5% in the placebo group; whereas bleeding occurred in 4% of patients in the nadroparin group and in no patients in the placebo group (P=0.0255). These data support the conclusion that not all IDDVT should receive full-dose anticoagulation. A practical therapeutic approach has recently been proposed (10), based on giving therapeutic anticoagulation for 3 months, as for proximal DVT, in patients with an unprovoked event or with other high-risk factors for VTE. A shorter treatment (4–6 weeks) with LMWH, even at lower anticoagulant doses, can be enough in patients who have low-risk conditions (11). Unfortunately, no data are still available on the use of DOACs in this clinical condition. Of notice, recent studies, based on long follow-up after stopping anticoagulation in patients with a first IDDVT, showed an incidence of recurrent VTE that was similar to that of patients with proximal DVT (12,13). Whether the occurrence of these long-term complications of ICDVT can be influenced by the initial treatment (anticoagulation yes or not, its type, dose, duration) remains to be assessed.

An interesting clinical study on treatment of patients with diagnosed ICDVT has recently been published (14). In the study the authors have retrospectively examined the cases of patients who had an ICDVT diagnosis with duplex ultrasonography during 4 years activity [2010–2013] at the Vascular Laboratory of the University of California. After the exclusion criteria, 384 patients were available for analysis (57.8% males; mean age 60±16 years), 222 of whom (57.5%) were inpatients. Therapeutic anticoagulation was prescribed to 243 patients (63.3%), the remaining non-treated patients were evaluated as controls. Significantly less patients received anticoagulation if admitted to a medical-surgical unit, had an operation or traumatic injury within prior 30 days, were in non-ambulatory status, or had received prophylactic anticoagulation during the 7 days before diagnosis of ICDVT. In contrast, the presence of acute medical illness, use of hormonal medications, presence of cancer and history of VTE were conditions associated with more prescription of anticoagulation. Proximal DVT or PE occurred in 13 control group patients (9.2%) and 8 anticoagulation group patients (3.3%). Intention to administer therapeutic anticoagulation was associated with a lower likelihood of proximal DVT or PE, with an RR of 0.36 (95% CI, 0.15–0.84). Clinically significant bleeding occurred more frequently in patients who received a prescription of therapeutic anticoagulation (8.6%) than in controls (2.2%; adjusted OR, 4.87; 95% CI, 1.37–17.3). On the basis of the high rate of clinically significant bleeding events associated with therapeutic anticoagulation the authors' conclusions are rather conservative. The conclude that: "*…therapeutic anticoagulation of patients with isolated calf DVTs may be warranted to reduce the risk for proximal venous thromboembolism. However, randomized studies are needed to draw firmer conclusions. Because the benefits of anticoagulation seem modest, we recommend attention to the risk for bleeding when determining whether anticoagulation is appropriate.*" I agree with this cautious conclusion. I am convinced that not all ICDVT are associated with the same risk of complications and not all deserve anticoagulation. The problem is that currently it is not sufficiently ascertained which ones are those at high or low risk. Furthermore, if anticoagulation is the preferred option, its intensity and duration are still uncertain. For sure prospective, controlled studies are urgently needed to reduce the risk of insufficient or excessive treatment in the high number of patients who present with ICDVT.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

References

1. Palareti G, Schellong S. Isolated distal deep vein thrombosis: what we know and what we are doing. J

Thromb Haemost 2012;10:11-9.
2. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest 2016;149:315-52.
3. NICE. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. Available online: https://www.nice.org.uk/guidance/cg144
4. Nicolaides AN, Fareed J, Kakkar AK, et al. Prevention and treatment of venous thromboembolism--International Consensus Statement. Int Angiol 2013;32:111-260.
5. Righini M, Paris S, Le Gal G, et al. Clinical relevance of distal deep vein thrombosis. Review of literature data. Thromb Haemost 2006;95:56-64.
6. Masuda EM, Kistner RL. The case for managing calf vein thrombi with duplex surveillance and selective anticoagulation. Dis Mon 2010;56:601-13.
7. Palareti G, Cosmi B, Lessiani G, et al. Evolution of untreated calf deep-vein thrombosis in high risk symptomatic outpatients: the blind, prospective CALTHRO study. Thromb Haemost 2010;104:1063-70.
8. Righini M, Bounameaux H. Clinical relevance of distal deep vein thrombosis. Curr Opin Pulm Med 2008;14:408-13.
9. Righini M, Galanaud JP, Guenneguez H, et al. Anticoagulant therapy for symptomatic calf deep vein thrombosis (CACTUS): a randomised, double-blind, placebo-controlled trial. Lancet Haematol 2016;3:e556-e562.
10. Palareti G. How I treat isolated distal deep vein thrombosis (IDDVT). Blood 2014;123:1802-9.
11. Parisi R, Visonà A, Camporese G, et al. Isolated distal deep vein thrombosis: efficacy and safety of a protocol of treatment. Treatment of Isolated Calf Thrombosis (TICT) Study. Int Angiol 2009;28:68-72.
12. Galanaud JP, Sevestre MA, Genty C, et al. Incidence and predictors of venous thromboembolism recurrence after a first isolated distal deep vein thrombosis. J Thromb Haemost 2014;12:436-43.
13. Sartori M, Migliaccio L, Favaretto E, et al. Two years outcome of isolated distal deep vein thrombosis. Thromb Res 2014;134:36-40.
14. Utter GH, Dhillon TS, Salcedo ES, et al. Therapeutic Anticoagulation for Isolated Calf Deep Vein Thrombosis. JAMA Surg 2016;151:e161770.

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