

# What's the Matter with Distal Deep Vein Thrombosis?

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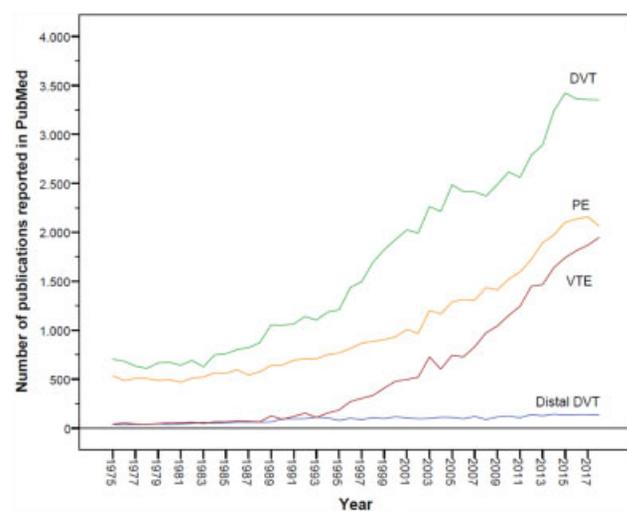
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Isolated distal deep vein thrombosis (IDDVT) refers to thrombi limited to the infrapopliteal deep (axial or muscular) veins of the lower limb. Although IDDVT represents a frequent finding in patients with suspected DVT,<sup>1</sup> it has long been considered the “poor cousin” of thromboembolic events occurring at other venous sites in light of its alleged benign course. Because of the general lack of interest for this condition, there is conspicuously little evidence in the literature supporting clinical decisions (►Fig. 1).<sup>2</sup> This in contrast to the vast literature dealing with the diagnosis and treatment of venous thromboembolism in general, essentially proximal DVT

(PDVT) and pulmonary embolism (PE).<sup>3–9</sup> It may not come as a surprise, therefore, that diagnostic and therapeutic practices for IDDVT vary across geographical regions.<sup>1,10,11</sup>

The work by Schellong et al<sup>12</sup> provides a comprehensive description of the clinical characteristics, treatment, and course of patients diagnosed with IDDVT, PDVT, or PE enrolled in the prospective, multinational, observational Global Anticoagulant Registry in the FIELD of Venous Thromboembolism (GARFIELD-VTE; NCT02155491).<sup>13</sup> In GARFIELD-VTE, 10,088 patients with a diagnosis of first or recurrent VTE and requiring anticoagulant treatment were included at more than 500 reference sites representative of VTE care for each of the 28 countries involved. The investigators captured data on baseline characteristics, treatment of acute VTE, hospitalizations, and clinical outcomes from the time of VTE diagnosis and during a 36-month follow-up period in the various care settings.<sup>13</sup>

One of the merits of this study is that it provides readers with an updated view of the way IDDVT is perceived and managed globally. The first striking result is the relative frequency of IDDVT diagnoses. The ratio of the number of patients with IDDVT to those with PDVT was 0.56 overall, corresponding to 56 patients being diagnosed with IDDVT every 100 PDVT diagnoses. However, extreme heterogeneity was observed across countries, with ratios ranging from 0.15 in Canada to 1.96 in Australia.<sup>12</sup> Indeed, these figures can by no means reflect the true proportion of IDDVT, since they represent probabilities conditional to the type of screening at each center, the diagnostic strategies adopted, and the eligibility criteria of GARFIELD-VTE, for example, being treated for VTE.<sup>13</sup> However, taking this into consideration, these results indicate that IDDVT can be frequently encountered in clinical practice and that dramatic variation exists in diagnostic patterns. This is entirely consistent with what was described more than a decade ago in an Italian survey of multiple specialized centers<sup>1</sup> and, more recently, reported in a systematic review and meta-analysis of cohort studies on



**Fig. 1** Publication trends illustrating the annual number of studies reported in PubMed for different manifestations of venous thromboembolism. The literature search strategy accounted for synonyms (e.g., ‘venous/vein’, or ‘calf/distal/muscular’), popular acronyms, and different combinations of keywords. DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

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isolated DVT.<sup>14</sup> In this perspective, it appears, nothing has changed.

Indeed, the authors emphasize that this variability may be due to the intrinsic nature of their study, which was designed to contribute a snapshot of current practices and, therefore, did not include standardized diagnostic algorithms or an overt definition of IDDVT.<sup>12</sup> These results indirectly highlight persisting uncertainty regarding (1) the anatomical level that defines “distal,” (2) whether the muscle veins should be considered part of the “deep” venous system, and (3) the nomenclature used to name distal (or calf) DVT in the literature.

In this context of ambiguity, both under- and overdiagnosis of IDDVT are plausible and explain such diverse ratios of IDDVT cases. Underdiagnosis may characterize those centers adopting a strategy based on compression ultrasound scan limited to proximal veins, which would only detect subsequent proximal extensions or PE. Overdiagnosis can be expected if bilateral whole-leg compression ultrasound is routinely performed, with obvious consequences for patients with asymptomatic events, who are then exposed to unnecessary anticoagulation.<sup>15,16</sup> An additional factor which likely influences the frequency of IDDVT diagnosis is represented by which professionals conduct diagnostic examinations. It has been shown that the accuracy achieved by trained vascular specialists, general practitioners, and nurses may vary,<sup>17</sup> and that there are discrepancies between scanning protocols adopted by different health care professionals.<sup>18</sup>

The GARFIELD-VTE also shows that only a tiny minority of patients with VTE were assessed for their pretest clinical probability of VTE or received D-dimer measurement.<sup>19</sup> This could be somehow expected for IDDVT, since prior studies demonstrated that diagnostic algorithms available for PDVT and PE are less accurate in patients with suspected IDDVT.<sup>20</sup> However, in the era of extensive use of VTE imaging techniques<sup>21</sup> and, concurrently, of the development of diagnostic algorithms designed to rationalize their use,<sup>22</sup> it is disappointing to observe that only 5% of the GARFIELD-VTE population underwent pretest assessment by standardized tools (e.g., the Wells' criteria).<sup>12</sup>

The present study supports prior observations suggesting that different manifestations of VTE have different etiologies. In GARFIELD-VTE, the authors confirm the potential link between IDDVT and distinct demographic characteristics or baseline risk factors, such as female sex, recent surgery or trauma, absence of cancer or prior VTE, and hormonal contraception.<sup>10,14,15,23</sup> Furthermore, they show that the rate of newly diagnosed cancer during 1-year follow-up was lower after acute IDDVT (1.3%) than after PDVT (2.5%) or PE (2.6%), therefore partially contradicting findings from a prospective multicenter cohort study conducted in France.<sup>24</sup>

In GARFIELD-VTE, the distribution of concomitant risk factors for VTE and the VTE location did not appear to influence the class of the anticoagulant prescribed to patients.<sup>12</sup> However, they had repercussions on the length of anticoagulation, which was shorter in patients with IDDVT (vs. PDVT or PE). It remains unclear, however, whether the

judgment of the individual risk of recurrence was primarily driven by the higher prevalence of transient provoking risk factors or by the distal location of DVT.

This fact indirectly raises the question whether IDDVT represents an independent positive prognostic factor for the risk of recurrence and death,<sup>25-27</sup> or if this correlation is mediated by the presence and severity of concomitant provoking risk factors for VTE.<sup>26,28</sup> The results of GARFIELD-VTE are in line with prior studies of patients with major persistent risk factors,<sup>29-31</sup> and show that the presence of cancer was the main determinant of outcomes. Indeed, the risk of recurrence within the first year after cancer-associated IDDVT was similar to that of patients with cancer-associated PDVT (sub-hazard ratio 1.05 adjusted for age and sex; 95% confidence interval 0.55–2.00) and high enough (~12–13%) in both groups to influence the decision to extend anticoagulation beyond the first 3 months. This may not be the case for patients with IDDVT caused by transient risk factors, who were characterized by a lower risk of recurrence than PDVT (hazard ratio 0.48 adjusted for age and sex; 95% confidence interval 0.30–0.78), amounting to a 1-year rate of 3.0%. Patients with unprovoked IDDVT had a risk of recurrence of 5.4%, similar to that of PDVT.<sup>12</sup>

We must recognize that the lack of central adjudication of clinical outcomes, the high prevalence (~15%) of patients with prior VTE, and the lack of adjustment for the duration of anticoagulation limit the interpretation of the results and further comparisons with prior studies focusing on first isolated DVT. While the best evidence concerning prognostic factors and efficacy of anticoagulant therapy still comes from prospective cohort studies<sup>26,27,30,32</sup> and randomized controlled trials,<sup>33</sup> the GARFIELD-VTE registry provides us with a clear take-home message. A standardized definition of IDDVT is needed, as well as a broader application of validated diagnostic algorithms and therapeutic schemes. Clear rules to better stratify patients with IDDVT based on their individual risk profile will have a major impact on the duration of anticoagulation.

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#### Conflict of Interest

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