Prevention of the Postthrombotic Syndrome with Anticoagulation: A Narrative Review

Ilia Makedonov1  Susan R. Kahn2  Jameel Abdulrehman3  Sam Schulman4  Aurelien Delluc5,6  Peter Gross7  Jean-Philippe Galanaud8

1Department of Medicine, Sunnybrook Health Sciences Center, Toronto, Ontario, Canada
2Department of Medicine and Lady Davis Institute, Jewish General Hospital, Montreal, Quebec, Canada
3Division of Hematology, Department of Medicine, University Health Network, University of Toronto, Toronto, Ontario, Canada
4Thrombosis and Atherosclerosis Research Institute, Department of Medicine, McMaster University, Hamilton, Ontario, Canada
5Ottawa Hospital Research Institute and University of Ottawa, Ottawa, Ontario, Canada
6Division of Hematology, Department of Medicine, The Ottawa Hospital and University of Ottawa, Ottawa, Ontario, Canada
7Department of Medicine, McMaster University and the Thrombosis and Atherosclerosis Research Institute, Hamilton, Ontario, Canada
8Department of Medicine, Sunnybrook Health Sciences Centre and University of Toronto, Toronto, Ontario, Canada

Address for correspondence Jean-Philippe Galanaud, MD, PHD, Department of Medicine, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue Room D 675 B, Toronto, Ontario CAN M4N 3M5, Canada (e-mail: Jean-Philippe.Galanaud@sunnybrook.ca).

Keywords
► postthrombotic syndrome
► venous thrombosis
► low molecular weight heparin
► vitamin K-dependent factors
► direct oral anticoagulants

Abstract
The postthrombotic syndrome (PTS) is chronic venous insufficiency secondary to a prior deep vein thrombosis (DVT). It is the most common complication of venous thromboembolism (VTE) and, while not fatal, it can lead to chronic, unremitting symptoms as well as societal and economic consequences. The cornerstone of PTS treatment lies in its prevention after DVT. Specific PTS preventative measures include the use of elastic compression stockings and pharmacomechanical catheter-directed thrombolysis. However, the efficacy of these treatments has been questioned by large randomized controlled trials (RCTs). So far, anticoagulation, primarily prescribed to prevent DVT extension and recurrence, appears to be the only unquestionably effective treatment for the prevention of PTS. In this literature review we present pathophysiological, biological, radiological, and clinical data supporting the efficacy of anticoagulants to prevent PTS and the possible differential efficacy among available classes of anticoagulants (vitamin K antagonists [VKAs], low molecular weight heparins [LMWHs] and direct oral anticoagulants [DOACs]). Data suggest that LMWHs and DOACs are superior to VKAs, but no head-to-head comparison is available between DOACs and LMWHs. Owing to their potentially greater anti-inflammatory properties, LMWHs could be superior to DOACs. This finding may be of interest particularly in patients with extensive DVT at high risk of moderate to severe PTS, but needs to be confirmed by a dedicated RCT.
Introduction

The postthrombotic syndrome (PTS) is chronic venous insufficiency (CVI) secondary to a prior deep vein thrombosis (DVT). PTS is the most common long-term complication of venous thromboembolism (VTE), developing in 20 to 50% of patients after a proximal DVT. While PTS is not lethal, it is an important public health issue as it has serious medical and economic consequences. It is a strong predictor of impaired quality of life and increased cost after a DVT. Indeed, PTS can lead to daily, nonremitting symptoms and, in severe cases, to venous ulcers. Patients with PTS report worse quality of life scores than patients with chronic diseases such as arthritis, chronic lung disease, and diabetes, whereas those with severe PTS can have a quality of life similar to patients with malignancy, angina, and congestive heart failure.

From a health economics point of view, PTS increases the cost of DVT treatment by 35 to 45% compared with uncomplicated DVT. Before 2014, in the absence of well-tolerated and effective treatments for established PTS, the cornerstone of PTS management was prevention with daily use of elastic compression stockings (ECS) for 2 years and, in selected cases, with catheter-directed thrombolyis (CDT) to treat acute DVT. More recently, after the SOX trial failed to show a benefit from ECS and the Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis (ATTRACT) trial failed to show a benefit from CDT, the efficacy of these treatments has been questioned and some doctors may be feeling “empty handed.” However, even if specific PTS preventative measures are ineffective or less effective than previously believed, it should be kept in mind that there exists a simple, effective, but nonspecific measure to prevent PTS: anticoagulant treatment. This is prescribed to all proximal DVT patients, primarily to prevent DVT extension, pulmonary embolism (PE), and VTE recurrence, but is also effective for preventing PTS. In this review, we will discuss the evidence supporting the effectiveness of anticoagulation for the prevention of PTS as well as associated mechanisms. We will also review whether the choice of anticoagulant may influence the risk of developing PTS and whether some anticoagulants could be favored over others with respect to PTS prevention.

Methods

We conducted a pubmed.gov and clinicaltrials.gov registry search (from inception up until December 8, 2020) to identify studies evaluating the effect of vitamin K antagonists (VKAs), low molecular weight heparins (LMWHs), and direct oral anticoagulants (DOACs) on PTS and comparing one anticoagulant to another with respect to PTS. The full search strategy is in Supplementary Appendix 1 (available in the online version). Only English, French, and Russian language literature was considered. References from all relevant papers were reviewed.

Effectiveness of Anticoagulation for Preventing PTS after DVT

Heparin (either unfractionated or, later, low molecular weight) for 7 to 10 days followed by a VKA was the standard of care for the treatment of VTE from the 1940s until the development of DOACs in the 21st century. A retrospective historical series from 1946 showed that anticoagulation reduced the signs and symptoms of PTS by a significant degree compared with no treatment. The presence of any swelling was reduced by 79%, induration and ulceration were both reduced by 100%, and the risk of heaviness decreased by 95%. While this was not a controlled study, it is suggestive of a profound effect of anticoagulation on the risk of PTS. Modern data also support the importance of therapeutic anticoagulation for the prevention of PTS. Patients who spend more than 50% of time beneath an international normalized ratio (INR) of 2.0 have a 2.71 odds ratio (OR) of developing PTS (1.44–5.1). Another study found that the OR of developing PTS was 1.94 (1.13–3.01) in patients with subtherapeutic INR values within the first 3 months of treatment. Although we would no longer be able to randomize anticoagulation against placebo in an acute proximal DVT treatment trial, a recent randomized controlled trial (RCT) included 178 patients with distal DVT and randomized them to either therapeutic LMWH (nadroparin) or placebo for 6 weeks. It showed that in the subgroup of patients without evidence of primary CVI, the rate of PTS at 6 years might be lower when treated with LMWH (9% vs. 24%, p = 0.04); however, this was a subgroup analysis. Current guidelines endorse good-quality anticoagulation as an effective tool for prevention of PTS but do not suggest a specific anticoagulant agent. Regarding the duration of anticoagulant treatment, there does not appear to be a benefit from extending anticoagulant treatment beyond the usual treatment duration with respect to PTS prevention. Thus, in the ExACT trial that randomized 281 patients with proximal VTE to receive either 3 months or 2 years of anticoagulation, there was no difference in terms of Villalta score or venous quality of life scores between groups at 2 years. Similarly, in the DURAC trial there was no difference in the rates of PTS at 10 years between patients treated with 6 weeks or 6 months of anticoagulation. In summary, both historic and modern data suggest that anticoagulation and quality of anticoagulation are critical at the acute phase of DVT for preventing PTS. This raises the question of the pathophysiological mechanism that could explain why anticoagulation prevents PTS after DVT.

Anticoagulation and PTS Pathophysiology

There is rapid thrombus regression during the first 2 to 3 months after the onset of anticoagulant treatment for acute DVT and, after 3 months, thrombus regression is gradual and slow. After 2 years, no additional thrombus regression is expected and the degree of residual venous obstruction (RVO) is fixed. From a hemodynamic point of
view, venous valvular reflux follows thrombus resolution and early thrombus resolution is associated with better valve preservation and reduced reflux.\textsuperscript{20} Furthermore, the smaller the clot burden, the lower the risks of RVO, venous reflex, and ultimately PTS.\textsuperscript{12} This is the rationale for the use of CDT in extensive DVT,\textsuperscript{21} but any treatment that is able to reduce the initial clot burden should reduce the risk of PTS. This is likely why all anticoagulation is effective for prevention of PTS.

In addition to RVO and venous reflex, there is also a significant inflammatory component to thrombus formation that is felt to contribute to PTS\textsuperscript{22} (\textit{\textsuperscript{→}Fig. 1}). The formation of a thrombus involves increased release of inflammatory cytokines (tissue necrosis factor-\(\alpha\) [TNF-\(\alpha\)], interleukin [IL]-6, IL-8), increased expression of adhesion molecules (P- and E-selectins, intercellular adhesion molecule 1 [ICAM-1], vascular cell adhesion molecule 1 [VCAM-1]), platelet and leukocyte adhesion, leukocyte migration into the vessel wall, and formation of neutrophil extracellular traps.\textsuperscript{23–26} From a hemodynamic point of view, higher levels of some inflammation markers have been associated with a reduced probability of venous recanalization (IL-6 and P-selectin)\textsuperscript{27} and with increased venous outflow resistance (IL-6).\textsuperscript{28} This translates clinically to a higher risk of PTS. Thus, in a Canadian study, elevated IL-6 levels were associated with an increased risk of PTS (OR 1.66 [1.05–2.62]).\textsuperscript{29} Similarly, the Bio-SOX study found that elevated levels of ICAM-1 and IL-10 were also predictive of an increased risk of PTS (relative risk [RR] 1.25 [1.05–1.48] and 1.27 [1.07–1.51], respectively).\textsuperscript{22} Importantly, there was a dose response between ICAM-1 level and the risk of PTS, providing support for a key role of inflammation in PTS development.\textsuperscript{22} In the same line, matrix metalloproteinases (MMPs), which are enzymes that regulate inflammatory mediators and maintain the integrity of physical barriers,\textsuperscript{23} have also be found to be associated with persistent thrombosis (MMP-9)\textsuperscript{30} and PTS (MMP-1 and MMP-8).\textsuperscript{31} In corroboration, animal models also showed that inflammation delayed thrombus resolution\textsuperscript{23,26} and promoted vein wall injury.\textsuperscript{32} Thus, therapies that reduce inflammation have the potential to improve thrombus resolution, vein wall remodeling, and to thereby prevent PTS. There is ongoing research to identify associated pathways, including in the pediatric population.\textsuperscript{33}

The inflammatory response is most strongly pronounced during the first month after acute VTE. The Bio-SOX study showed that inflammatory markers (C-reactive protein, IL-6) rapidly decreased during the first month after diagnosis, and only marginally decreased over the five subsequent months.\textsuperscript{22} Additionally, baseline inflammatory marker elevation predicted subsequent PTS.\textsuperscript{22} This suggests that an anticoagulant with potent anti-inflammatory properties would provide the most benefit during the first month of treatment (\textit{\textsuperscript{→}Fig. 1}).

By reducing clot extension, anticoagulants may prevent RVO and venous reflex, two important components of PTS physiopathology. Anticoagulants may to some degree also influence the third component of PTS pathophysiology: inflammation. The differential impact on inflammation of the various types of anticoagulants might translate to

\begin{itemize}
\item TNF-\(\alpha\): promotes monocyte/macrophage infiltration and cytokine production,
\item IL-6: stimulates inflammatory cytokine production and promotes adhesion molecule expression,
\item IL-8: recruits neutrophils and activates inflammation.
\end{itemize}

\textbf{Fig. 1} Inflammatory cytokines are predisposing factors for VTE (e.g., IL6, IL 8, TNF-\(\alpha\)) and can activate monocytes, induce P- and L-selectin pathways, promote release of VWF, increase platelet production, and promote neutrophil infiltration. TAM family receptor tyrosine kinases (TAM RTKs) inhibit inflammatory signaling, and are found on the surface of monocytes, macrophages, and other cells. Activated monocytes propagate the coagulation cascade through tissue factor synthesis and production of microparticles. These in turn adhere to selectin receptors found on both platelets and endothelial cells. MMPs affect thrombus resolution and collagen formation. MMP-9 may increase the stiffness of remodeled venous walls. VKAs may promote coagulation through their inhibition of the TAM RTKs. TFN-\(\alpha\) levels are decreased by both LMWHs and DOACs. IL-6 and IL-8 levels are reduced by DOACs. Neutrophilic infiltration and selectin pathways are inhibited by LMWHs. TF synthesis is reduced by LMWHs and DOACs. MMP-9 levels are reduced by both LMWHs and DOACs. DOAC, direct oral anticoagulant; IL6, interleukin 6; IL 8, interleukin 8; LMWH, low molecular weight heparin; MMP, matrix metalloproteinase; TAM, Tyro3, Axl and Mer; TNF-\(\alpha\), tumor necrosis factor \(\alpha\); VKA, vitamin K antagonist; VTE, venous thromboembolism; VWF, von Willebrand factor.
differential effectiveness in PTS prevention. In the next section, we will review, for each class of anticoagulant (VKAs, LMWHs, and DOACs), their impact on inflammation as well as the radiologic and clinical evidence supporting their variable efficacy for prevention of PTS.

**Vitamin K Antagonists**

VKAs reduce the amount of active vitamin K available for the synthesis of vitamin K-dependent clotting factors. Vitamin K is also used in pathways involving the TAM receptor tyrosine kinases (RTKs), which are distinct from the coagulation cascade. VKAs may influence inflammation by inhibiting growth-arrest-specific 6, which activates several RTKs (MERTK and AXL). MERTK and AXL inhibit the innate immune system, including monocyte activity. Monocytes play an important proinflammatory role in acute VTE, preventing thrombus maturation and resolution. Therefore, from a theoretical point of view, by reducing the activation of RTKs, VKA may reduce fibrinolysis and collagenolysis. Murine models have shown increased systemic and local levels of inflammatory markers such as IL-6, IL-17, and interferon-γ after exposure to VKAs, although the results have not been consistent. A recent literature review suggests that VKAs are favored to be proinflammatory. Anticoagulants that do not possess such proinflammatory properties or those that have anti-inflammatory properties are likely to be potentially more effective than VKAs with respect to PTS prevention.

**Low Molecular Weight Heparins**

**Impact of LMWHs on Inflammation**

LMWHs are linear polysaccharide structures, and have been used clinically since the 1980s. They are derivatives of unfractionated heparin (UFH), which originates from mast cells found predominantly in porcine and bovine intestinal mucosa. Both heparin and LMWHs have strong anti-inflammatory properties, owing to their glycan chains. LMWHs release tissue factor pathway inhibitor (TFPI), block P-selectin interactions, and inhibit lymphocytes, chemokines, fibroblast proliferation, endothelial activation, and neoangiogenesis. Experimental rodent models of DVT have reported that LMWH reduced the size of the clot and inflammatory cell extravasation into the vein compared with controls, and was found to have a protective effect on the vein wall by promoting re-endothelialization and reducing fibrosis and intimal hyperplasia. Importantly, there was a dose–response effect, with greater benefits with higher doses of LMWH, suggesting a true biological effect. As compared with VKA, in a RCT of 1,048 patients with acute DVT, treatment with LMWH (reviparin) significantly reduced the inflammatory response at 21 days, as reflected by higher levels of TFPI, and lower levels of fibrinogen and of thrombin activatable fibrinolysis inhibitor. These laboratory data suggest that, unlike VKAs, LMWHs have strong anti-inflammatory properties which could theoretically lead to better effectiveness in PTS prevention.

**Radiologic Evidence of LMWH versus VKA Effectiveness for PTS Prevention**

Radiologic data suggests that LMWH use results in higher recanalization rates than VKA use. There have been six randomized trials that compared VKAs to various doses of LMWHs and assessed radiologic outcomes. Three of these used prophylactic dosing and the other three used therapeutic dosing. Patient numbers ranged from 105 to 324, and LMWH treatment duration ranged between 3 and 6 months. The trials that used prophylactic dosing for extended treatment all had an upfront period of 7 to 10 days of either UFH or full dosing LMWH. Five of the six trials found either more complete or more rapid recanalization in the LMWH arm, and one meta-analysis of 1,006 patients also found improved recanalization with LMWH (RR 0.49 [0.26–0.92] and RR 0.73 [0.53–1.01] for therapeutic and prophylactic dosing, respectively). However, heterogeneity across studies was significant, reducing the quality of the data. Interestingly, the improved recanalization rate was not associated with reduced rates of VTE recurrence, suggesting that mechanisms other than VTE recurrence accounted for the protective effect.

**Clinical Evidence of LMWH versus VKA Effectiveness for PTS Prevention**

There have been four randomized trials comparing LMWHs to VKAs with respect to PTS prevention, with one using prophylactic dosing, and the other three using therapeutic dosing. Patient numbers ranged between 100 and 480, and treatment duration with LMWH was between 3 and 6 months. One of the trials used the Villalba scale to quantify PTS, two trials used nonvalidated clinical observations, and the fourth trial used a self-reported patient scale. The three smaller trials favored LMWH in terms of lower PTS rates, but results did not reach statistical significance. The largest trial reported a statistically significant reduction in PTS with LMWH at 12 weeks (OR = 0.77 [0.66–0.91], p = 0.001). This was a multicenter Canadian trial that randomized patients to 3 months of tinzaparin or a VKA, and included 480 patients. The presence of PTS was evaluated at 12 weeks, and the presence of ulcers was evaluated at 12 weeks and 1 year. Unfortunately, the proportion of iliac and common femoral vein DVTs and the extent of INR control were not documented. A meta-analysis was not able to combine PTS outcomes due to the variable follow-up periods (3 months–5 years) and variable assessment methods, but it did compare the risk of venous ulcers. Based on two studies, the risk of venous ulcers, which represent the most severe form of PTS, was significantly and strongly reduced with LMWH (RR 0.31 [0.02–0.71], p = 0.019).

See Table 1 for a summary of the studies.

**Summary**

Unlike VKAs, LMWHs have strong anti-inflammatory properties. Animal models have shown a favorable effect of LMWHs on the natural history of thrombosis, with more rapid resolution, faster re-endothelialization, and reduced fibrosis. Radiologic data in human patients have shown...
Table 1 Randomized trials comparing either radiologic recanalization rates or rates of clinical PTS or both between LMWH treatment (i.e., monotherapy) and VKA treatment

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Number of patients (total [LMWH/VKA groups])</th>
<th>LMWH (dosing and duration; prophylactic/therapeutic dose)</th>
<th>Follow-up</th>
<th>Outcomes (LMWH/VKA groups)</th>
<th>Study type (radiologic, PTS, both)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Das et al (1996)</td>
<td>105 (50/55)</td>
<td>Dalteparin (UFH × 10 days then dalteparin 5000 IU qd × 3 mo; prophylactic)</td>
<td>9 mo</td>
<td>Recanalization in 80%/83% (NS)</td>
<td>Radiologic</td>
</tr>
<tr>
<td>López-Beret et al (2001)</td>
<td>158 (81/77)</td>
<td>Nadroparin (1025 IU/10 kg bid × 3–6 mo; therapeutic)</td>
<td>1–12 mo</td>
<td>Recanalization in 63.9%/19.3%, 66.7%/14.6%, and 62%/27.5% in the CFV, SFVF, and PV, respectively (p &lt; 0.001)</td>
<td>Radiologic</td>
</tr>
<tr>
<td>Kakkar et al (2003)</td>
<td>297 (199*/98b)</td>
<td>Bemiparin (115 IU/kg qd × 7 days then VKA in group B or 115 IU/kg qd × 10 days than 3500 IU qd in group C, therapeutic dose upfront followed by prophylactic)</td>
<td>14 days– 12 wk</td>
<td>Improved Marder score in 72%/52% (p &lt; 0.005) at 14 days; recanalization in 75.3%/81% at 12 wk (NS)</td>
<td>Radiologic</td>
</tr>
<tr>
<td>Hull et al (2009)</td>
<td>480 (240/240)</td>
<td>Tinzaparin (175 IU/kg qd × 12 wk; therapeutic)</td>
<td>3 mo, 1 y</td>
<td>OR 0.77 at 12 wk for development of PTS, favoring LMWH (p = 0.001). Ulcers in 0.5%/4.1% (p = 0.02) at 1 y</td>
<td>PTS</td>
</tr>
<tr>
<td>Romera et al (2009)</td>
<td>241 (119/122c)</td>
<td>Tinzaparin (175 IU/kg qd until INR &gt; 2 then VKA or 175 IU/kg qd × 6 mo; therapeutic)</td>
<td>6–12 mo</td>
<td>Recanalization in 73.1%/47.5%, 91.5%/69.2% at 6 and 12 mo, respectively (p &lt; 0.001). Edema in 13.4%/13.9%, local pain or tenderness in 0%/1.6% (NS) at 6 mo</td>
<td>Both</td>
</tr>
<tr>
<td>Gonzalez-Fajardo et al (1999, 2008)</td>
<td>165 (85/80) in 1999 100 (56/44) in 2008</td>
<td>Enoxaparin (40 mg bid × 7 days than 40 mg qd × 3 mo; prophylactic)</td>
<td>3 mo–5 y</td>
<td>Marder score improved by 49.1%/24.5% (p &lt; 0.001) at 3 mo. PTS absent in 39.3%/29.5% (NS) at 5 y</td>
<td>Both</td>
</tr>
<tr>
<td>Daskalopoulos et al (2005)</td>
<td>108 (55/53)</td>
<td>Tinzaparin (175 IU/kg qd × 6 mo; therapeutic)</td>
<td>1–12 mo</td>
<td>Marder score 9/10 (p = 0.017), 6.5/8 (p = 0.013), 5/7 (p = 0.011) at 3, 6, and 12 mo, respectively. Edema in 32%/34.6%, local pain or tenderness in 18%/15.4%, skin changes in 14%/19.2%, ulcer in 0%/5.8% (NS) at 12 mo</td>
<td>Both</td>
</tr>
</tbody>
</table>

Abbreviations: bid, twice a day; CFV, common femoral vein; INR, international normalized ratio; LMWH, low molecular weight heparin; NS, not significant; OR, odds ratio; PTS, postthrombotic syndrome; PV, popliteal vein; qd, once a day; SFVF, superficial femoral vein; UFH, unfractionated heparin; VKA, vitamin K antagonist.

*Group B received therapeutic LMWH × 7 days followed by VKA whereas group C received therapeutic LMWH × 10 days followed by prophylactic LMWH.

*Group A received UFH followed by VKA.

*These patients received upfront LMWH until the VKA was therapeutic.
improved recanalization rates with LMWHs compared with VKAs, independent of VTE recurrence rates. While there are few RCTs, they do report a significant reduction in PTS risk after extended treatment of DVT with LMWH. The mechanisms for this may relate to nonanticoagulant properties of LMWHs.

Direct Oral Anticoaguants

Impact of DOAC on Inflammation

DOACs are synthetic molecules that inhibit factors IIa or Xa. Laboratory evidence suggests that they also target inflammatory pathways. Murine data shows that rivaroxaban decreases infarct size in a model of myocardial infarction and reduces the release of inflammatory markers (IL-6, TNF-α, MMP-9) in models of atherosclerosis. Human vascular endothelial cell models of oxidative damage have shown an increased release of IL-10, a potent anti-inflammatory cytokine, and reduced expression of inflammatory genes (VCAM-1, ICAM-1, IL-8, TF). A human monocyte model showed reduced release of inflammatory cytokines (IL-6) and chemokines (IL-8, monocyte chemoattractant protein-1) from cells activated by thrombin. A human plasma proteomics study showed that rivaroxaban increased thrombomodulin levels and showed a trend to decreased MMP-9 levels. However, there is an absence of studies that used DVT models, and most of the data originates from cell lines. Therefore, the relevance of these findings to PTS is less clear than it is for LMWHs.

Radiologic Evidence of DOAC versus VKA Effectiveness for PTS Prevention

Four retrospective studies and one RCT have compared vein recanalization rates in patients treated with DOACs and VKAs. Most of these studies investigated rivaroxaban. All five studies showed reduced rates of RVO with DOAC treatment, but one study did not reach statistical significance. Most studies reported outcomes at 3 to 12 months after index DVT, but Ferreira et al evaluated patients much later after the index VTE. However, there is an absence of studies that used DVT models, and most of the data originates from cell lines. Therefore, the relevance of these findings to PTS is less clear than it is for LMWHs.

Clinical Evidence of DOAC versus VKA Effectiveness for PTS Prevention

There have been four retrospective studies, two cross-sectional follow-up studies of the phase III DOAC trials, two registry-based studies, and one recent RCT comparing DOACs to VKAs for PTS. A recent meta-analysis included all of the above studies except for the RE-COVER follow-up study (the phase III study of dabigatran compared with warfarin) and the registry-based studies. The retrospective studies ranged in size from 100 to 1,300 patients, and the registry studies included 20,000 to 37,000 patients. The DOAC employed in all follow-up studies was rivaroxaban, except for the RE-COVER follow-up study, which evaluated dabigatran. All the rivaroxaban studies reported a lower risk of PTS with rivaroxaban compared with VKA. The RE-COVER follow-up study did not show a difference between dabigatran and VKA in regards to PTS risk, and this study also employed the patient self-reported Villalta scale (while all other studies used the patient- and clinician-rated Villalta scale). The meta-analysis showed a protective effect of rivaroxaban compared with VKA on risk of PTS (adjusted OR = 0.44 [0.35–0.56]; I² = 0 with p = 0.42). The RE-COVER follow-up study showed overall higher rates of PTS, with 61% of patients in the DVT group and 44% of the patients in the PE-only group diagnosed with PTS at a mean follow-up of 8.7 years. These findings suggest that treatment-related effects may have been masked by naturally progressive baseline CVI, as PTS observed in patients in the PE-only group was more likely to be attributed to underlying CVI. Among registry studies, Coleman et al found a reduced risk of PTS with rivaroxaban treatment (23% relative reduction [95% confidence interval 16–30%]) and Segard et al found a nonsignificant trend to reduced PTS with rivaroxaban (HR = 0.88 [0.66–1.17]). However, registry studies are based on diagnostic codes, and it is difficult to accurately capture a diagnosis as nuanced as PTS based on coding. The RCT by de Athayde Soares et al is unique in having randomized patients to DOAC versus VKA specifically to assess effect on PTS. Eighty-four patients were randomized to rivaroxaban versus VKA for 6 months, and the median follow-up time was 360 days. The study showed a lower risk of PTS with rivaroxaban than VKA at 360 days (8.7% vs. 28.9%, p < 0.001). However, there were significantly more patients with proximal DVT in the VKA group (23.9% vs. 5.3% iliofemoral, p = 0.018), which may have favored the rivaroxaban group. In the VKA group, there was good adherence to INR monitoring, with 95% of patients in the therapeutic range, and a median INR of 2.4. This suggests that the protective effect of rivaroxaban was not due to higher quality anticoagulation than the VKA group. This was a single-center trial, and the results require confirmation. Further, the authors’ reporting of time in therapeutic range was not conventional, and was not clearly defined. Several observational studies are ongoing regarding the real-world incidence of PTS with DOACs, including the Italian Monitoring Anticoagulant Therapy Observational Study (MAC Project), which aims to recruit up to 4,000 Italian VTE patients. Current data supports the superiority of DOACs over VKAs for prevention of PTS, although among DOACs, rivaroxaban has been nearly exclusively studied, and data on other DOACs is lacking.
Clinical Evidence of LMWH versus DOAC Effectiveness for PTS Prevention

As presented above, both LMWHs and DOACs appear to be more effective than VKAs for preventing PTS. DOACs are the current standard of care for the treatment of most patients with acute DVT, but no trial to date has compared LMWH to DOAC therapy for the prevention of PTS. In vitro laboratory data suggest that LMWHs may be more potent at inhibiting thrombin generation, delaying clot formation, and reducing maximum clot firmness than DOACs. While this is not readily translatable to clinical outcomes, it suggests that LMWHs may reduce the thrombotic and inflammatory burden in the acute phase of DVT compared with DOACs. Several experts in the field have called for trials comparing the efficacy of LMWHs to DOACs for prevention of PTS. As outlined previously, the inflammatory response is greatest in the first month following VTE, and patients with greater inflammatory changes at baseline are more likely to develop PTS. See Fig. 2 for a hypothetical management pathway that takes into account the possible benefits of upfront LMWH treatment; high-risk patients can be classified based on clinical experience and PTS prediction models.

Fig. 2 Hypothetical management pathway for proximal deep vein thrombosis (DVT). The SOX-PTS, Amin, and Méan models predict the risk of PTS. Iliofemoral DVT has also been associated with an increased risk of PTS (odds ratio [OR] 6.3 [2.0–19.8]). Risk is calculated in the models as follows: SOX-PTS model: 0 points—6.4%, 1 point—13.4%, 2 points—16.4%, 3 points—25%, ≥4 points—30% risk of PTS; Amin model: 0–2 points—10%, 3–4 points—20%, ≥5 points—40% risk of PTS; Méan model: 0–3 points—24.4%, 4–5 points—38.4%, ≥6 points—80.7%. Please refer to the original publications regarding assignment of points. BMI, body mass index; LMWH, low molecular weight heparin; OAC, oral anticoagulant; PTS, postthrombotic syndrome.
course of up to 4 weeks of a LMWH to upfront DOAC treatment. Such a design appears pragmatic as patients in the noncancer setting may be averse to committing to 3 to 6 months of an injectable formulation for uncertain benefit with respect to PTS.

**Conclusion**

Timely and effective anticoagulant treatment constitutes, so far, the best way to prevent PTS after an acute DVT. Data suggest that both LMWHs and DOACs could be superior to VKAs for the prevention of PTS. This improved efficacy could be driven by LMWH and DOAC anti-inflammatory properties. LMWHs appear to have more potent anti-inflammatory properties than DOACs but no head-to-head comparison exists with respect to PTS prevention. Such an assessment is desirable, particularly in patients with extensive DVT, where the inflammatory response and risk of PTS are the highest. The TILE study will try to answer that question (ClinicalTrials.gov NCT04794569).

Conflict of Interest

J.P.G. received consultant fees from Sanofi S.A. and Servier Laboratories; research grants from Leo Pharma, Bayer AG, and Bristol-Myers Squibb-Pfizer; and a travel grant from Innothéra. Other authors have no conflicts to declare.

**References**