Circulation

AHA SCIENTIFIC STATEMENT

Revisiting the Open Vein Hypothesis to Reduce the Postthrombotic Syndrome: Implications for Multidisciplinary Care and Research: A Scientific Statement From the American Heart Association

This statement is endorsed by the Shanghai Aging and Degenerative Disease Society; Society for Vascular Medicine; and Society of Interventional Radiology

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ABSTRACT: The "open vein hypothesis" postulates that early thrombus clearance and restoration of venous blood flow may prevent postthrombotic syndrome after proximal deep vein thrombosis. Since its proposal several decades ago, new insights from basic and clinical studies have motivated a re-evaluation and refinement of this hypothesis. According to data from these studies, susceptibility to postthrombotic syndrome occurs as a result of differences in genetic composition, thrombophilic conditions, predilection to inflammation and fibrosis, endogenous fibrinolytic capability, timing of symptom presentation and treatment initiation, and efficacy of antithrombotic therapy. Although initial restoration of an open vein appears to be beneficial for selected patient groups, freedom from postthrombotic syndrome is more likely in the setting of long-term venous patency, reduced recurrent thrombotic episodes, and reduced perithrombotic (eg, vein wall and valve) inflammation. These underlying biological mechanisms need further elucidation, with a long-term goal of personalizing treatment by mapping the individuals' clinical presentation with their underlying risk factors and assessing time-dependent biological processes that occur as a clinical venous thrombosis resolves. This scientific statement (1) highlights historical fundamentals of the open vein hypothesis and then showcases new research insights into the pathophysiological factors driving postthrombotic syndrome; (2) discusses advantages and disadvantages of imaging modalities for deep vein thrombosis used in clinical practice, including the potential to depict thrombus chronicity and status of vein wall injury; (3) proposes measures to develop integrated multidisciplinary care for deep vein thrombosis focused on the reduction of postthrombotic syndrome; and (4) identifies priority areas and questions for further research.

Key Words: AHA Scientific Statements ■ antithrombotic agents ■ deep vein thrombosis ■ inflammation ■ multidisciplinary care ■ postthrombotic syndrome ■ venous revascularization

Postthrombotic syndrome (PTS) refers to the clinical condition of chronic venous disease that develops after a deep vein thrombosis (DVT) in the upper or lower extremity, with symptoms and signs ranging from limb aching, swelling, and hyperpigmentation to skin ulceration.[1,2] Despite optimal treatment with anticoagulation and compression, 20% to 50% of patients with lower-extremity DVT develop PTS globally, and ≈5% of patients with DVT are estimated to develop severe PTS in the long term.[1,3,4] Overall, PTS substantially reduces health-related quality of life (QOL) and increases health care expenditures.[1,3]

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The management of established PTS is challenging and varies considerably across clinical practices. Commonly used measures include compression therapy; lifestyle measures such as leg elevation, weight loss, and exercise; and wound care (for patients with venous ulcers).[2,3,5,6] Venoactive drugs may provide short-term relief of PTS symptoms, but their long-term effectiveness and safety are unknown.[3,5,6] Although these measures may alleviate PTS symptoms in some patients, they are not curative, and many patients continue to have debilitating symptoms, functional limitations, and suboptimal QOL.[3,5,6]

Therefore, prevention of PTS is an important, desired goal of DVT treatment. However, beyond anticoagulation, there are no consistently effective, evidence-based approaches to prevent PTS.[3,7] Elastic compression stockings (ECS) continue to be used to reduce DVT symptoms, but their efficacy for PTS prevention is unclear.[8,9] Emerging studies suggest that drugs with anti-inflammatory properties (eg, statins and low-molecular-weight heparin) may prevent PTS, but large clinical trials have not yet provided supportive data.[10–12]

The continued high prevalence of PTS and its most burdensome manifestations has inspired further attempts to prevent PTS based on the open vein hypothesis (OVH).[13,14] This hypothesis postulates that early thrombus clearance and restoration of unobstructed deep venous blood flow will reduce the risk of PTS through a reduction of late residual obstruction and valvular reflux, 2 drivers of venous hypertension and PTS.[13,14] However, in 3 multicenter randomized controlled trials (RCTs), the effects of rapid thrombus removal with endovascular interventions in reducing PTS after acute proximal DVT compared with anticoagulation alone ranged from neutral to modestly beneficial.[15–17] In the largest trial, the benefits of rapid thrombus removal on PTS severity and QOL occurred mainly in patients with iliofemoral DVT (IFDVT) but not in patients with DVT limited only to the femoropopliteal veins.[18,19] In addition, recent data have suggested that the timing of restoration of blood flow through endogenous or exogenous fibrinolysis, concomitant venous inflammatory and fibrotic changes, and interventional thrombus removal may also influence the ability to prevent or reduce pathophysiological drivers of PTS.[20,21]

Therefore, the goals of this scientific statement are (1) to integrate historical knowledge with recent research findings to frame current scientific understanding of the pathophysiological factors driving PTS after proximal lower-extremity DVT, with particular reference to the OVH; (2) to discuss new and existing ways to comprehensively image thrombus extent, venous patency, flow parameters, valve function, thrombus chronicity, and status of vein wall injury; (3) to propose measures to strengthen multidisciplinary teams to focus on reducing PTS, with particular attention to patients with IFDVT; and (4) to further identify priority research areas and questions that must be addressed to achieve transformative change to reduce PTS occurrence and severity, from DVT prevention to PTS management. Because most of the insight on the biology of PTS is derived from studies of lower-extremity DVT and because severe PTS manifestations are more common in the lower limbs, this scientific statement focuses on reduction of PTS in the lower anatomical territory. Figure 1 shows the central illustration of this scientific statement.

METHOD

The details of panel formation, literature review, scientific statement development and consensus are described in the Supplemental Material.

REVISITING THE OVH

The OVH was first evaluated in clinical DVT studies comparing systemic urokinase or streptokinase with systemic anticoagulation in the 1960s, followed by studies focused on systemic fibrinolysis and surgical thrombectomy in the 1970s and 1980s.[22–24] In early ultrasound studies that evaluated the natural history of DVT in anticoagulated patients, it was observed that thrombus clearance was often incomplete, that vein segments showing slower endogenous clot clearance were more likely to develop valvular reflux, and that valvular reflux developed less frequently in veins that remained free from DVT propagation or rethrombosis.[25,26] In a more recent RCT that evaluated the effects of ECS, patients with acute proximal DVT who had residual thrombus or popliteal vein valvular reflux on ultrasound at the 6-month follow-up were more likely to develop PTS.[27] In other studies, including a meta-analysis of 11 RCTs, patients with greater residual thrombus after a course of anticoagulant therapy were significantly more likely to develop recurrent DVT, a major risk factor for PTS.[28–31]

Several studies have identified patients with acute IFDVT as a high-risk subgroup for developing PTS.[28,32] IFDVT is defined as complete or partial thrombosis of any part of the iliac vein or the common femoral vein, with or without involvement of other veins.[33,34] The acute phase of IFDVT was empirically defined as the time when the patient's symptom duration is ≤14 days or imaging studies indicate that the thrombosis occurred ≤14 days ago.[33,34] IFDVT represents approximately a quarter of all lower-extremity DVTs.[18,32] In the short term, IFDVT can be associated with a high risk of pulmonary embolism (PE) and severe lower-extremity symptoms; and rarely presents as acute leg ischemia in those presenting with phlegmasia cerulea dolens.[33,34] In the long term, patients with IFDVT have a higher risk for any PTS, severe PTS, and more frequent recurrent VTE compared with patients with less extensive DVTs.[1,18,19,28,32,35] Among those initially presenting patients with IFDVT, ≈50% develop any PTS, up to 40% develop some degree of venous claudication, ≈25% develop moderate to severe PTS, and up to 10% develop severe PTS that may include venous ulceration.[1,18,32,35]

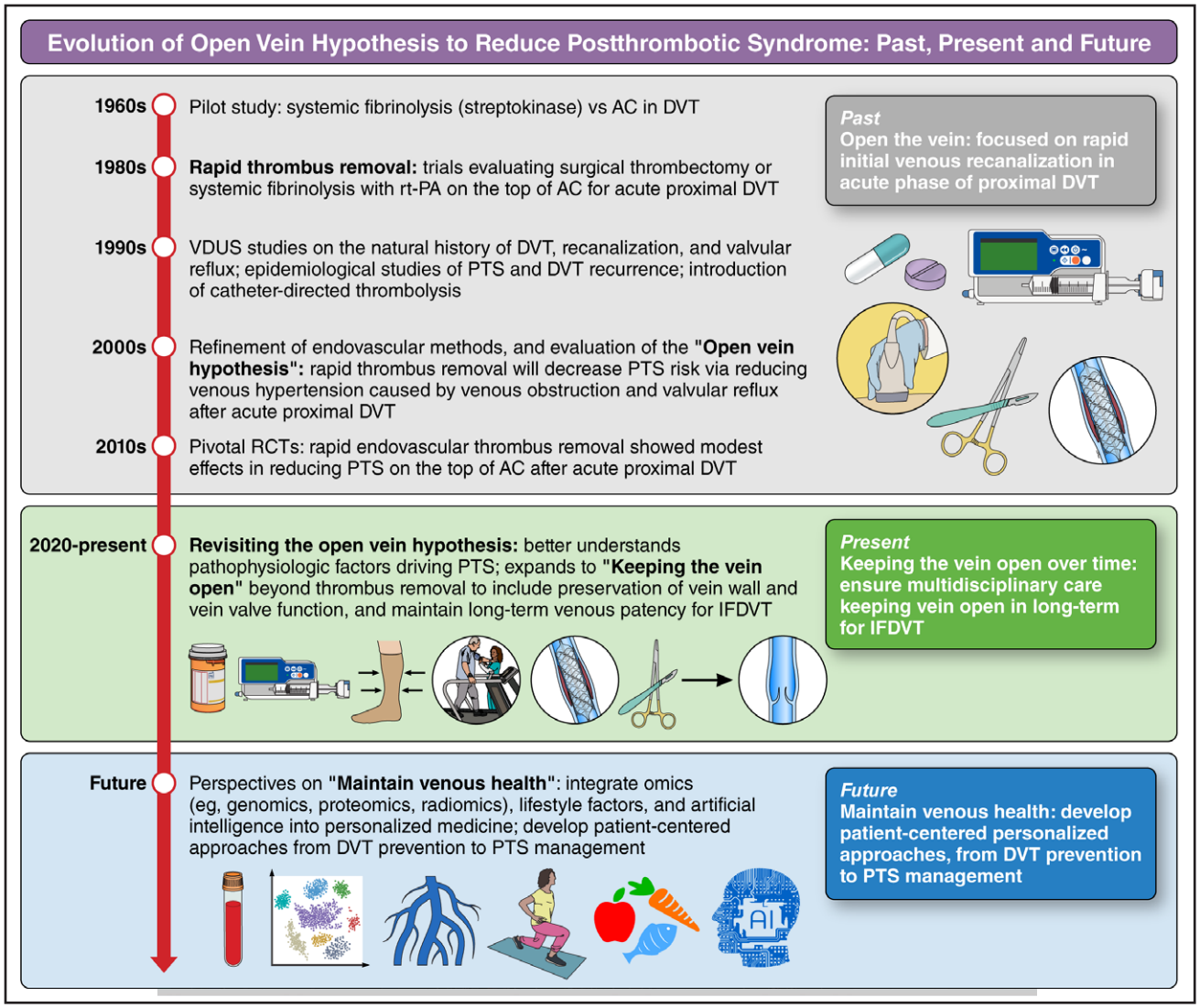

Figure 1. Evolution of OVH to reduce PTS: past, present and future.
The open vein hypothesis (OVH) was revisited and refined longitudinally. In the past, the OVH focused on rapid initial venous recanalization in the acute phase of proximal deep vein thrombosis (DVT). At present, the hypothesis is refined to reflect greater understanding that reducing postthrombotic syndrome (PTS) will require keeping the vein open over time; addressing other mechanisms of PTS development, including inflammation; and ensuring multidisciplinary care for patients with iliofemoral DVT (IFDVT). In the future, with the development of omics and artificial intelligence, perspectives on patient-centered personalized approaches from DVT prevention to PTS management may evolve, and the hypothesis could be refined further to encompass a broader range of strategies to holistically maintain venous health. AC indicates anticoagulation; rt-PA, recombinant tissue-type plasminogen activator; and VDUS, venous duplex ultrasound.

The aforementioned mechanistic and epidemiological observations have been bolstered by preliminary clinical studies evaluating active thrombus removal strategies for DVT. Historically, systemic fibrinolytic therapy was found to achieve >50% clot lysis (by quantitative analysis of venograms) more frequently than heparin alone (62% versus 17%, respectively; $P<0.0001$).[22] The benefit of fibrinolysis came at the cost of an increase in bleeding complications, which included hemorrhagic strokes.[22,36] A few small follow-up studies suggested the presence of long-term reductions in PTS in the lysed patients.[37–39] Similar observations were made in studies of surgical thrombectomy and intrathrombus infusion catheter-directed thrombolysis (CDT).[24,40–44]

Most of these treatment-focused studies had major methodological limitations, including small sample sizes, use of unvalidated PTS measures, and lack of blinding of clinical outcome assessments. Because CDT and related interventional approaches carry a potential for increased risks and costs, 3 multicenter RCTs were conducted between 2007 and 2018 to determine whether their routine use could reduce PTS with acceptable safety.[15–17] Strengths of these studies included robust multidisciplinary participation; use of contemporary CDT methods and validated measures of PTS; and systematic precautions against bias such as central randomization, rigorous data monitoring, and blinded clinical and imaging outcome assessments.[15–17] Limitations included their

open-label design (patients were not blinded); low to medium statistical power, especially for secondary outcomes; heterogeneity of the endovascular treatments studied; losses to follow-up; limited imaging follow-up and duration of clinical follow-up (2–5 years); and lack of blood specimen collection to permit proteomic, genetic, and other biomarker analyses.[15–17] Furthermore, contemporary therapeutic modalities such as direct oral anticoagulants, intravascular ultrasound (IVUS), and dedicated venous stents were not routinely used in these trials.[15–17]

Overall, the results of these interventional trials on PTS-related end points were mixed and did not provide compelling evidence of benefit to justify large-scale adoption of routine catheter intervention for acute proximal DVT. Only 1 of 3 three trials, CaVenT (Catheter-Directed Venous Thrombolysis Study; NCT00251771), found CDT to produce a reduction of PTS incidence at 2 years (15% absolute risk reduction) that further increased at 5 years but without achieving an improvement in long-term QOL.[15,45,46] In the largest study of 692 patients with acute proximal DVT, the ATTRACT trial (Acute Venous Thrombosis: Thrombus Removal With Adjunctive Catheter-Directed Thrombolysis; NCT00790335), pharmaco-mechanical CDT (PCDT) did not benefit patients who presented with DVT limited to the femoropopliteal venous segments.[19] However, in patients with acute IFDVT, PCDT significantly reduced PTS severity, improved resolution of presenting limb pain and swelling, and improved early and late venous disease-specific QOL.[18,47] It is important to note that the patients with IFDVT with more severe symptoms at DVT presentation appeared to experience the largest reductions in PTS severity with PCDT.[48] However, the CAVA trial (Catheter-Directed Thrombolysis Versus Anticoagulation Trial; NCT00970619) found that ultrasound-assisted CDT provided no additional benefit in PTS occurrence or QOL at 1 year in patients with acute IFDVT.[17] At 3 years, CDT provided no additional improvement of QOL and no significant reduction (14.2% absolute risk reduction; P=0.11) of PTS occurrence with the prespecified Villalta scoring method; when the International Society on Thrombosis and Haemostasis–recommended scoring was used, a 22% absolute risk reduction (P=0.01) was observed.[49,50] After these RCTs, new updates to Society of Interventional Radiology societal position statements, European Society for Vascular Surgery practice guidelines, and American Society of Hematology guidelines demonstrated increased comfort with the use of CDT/PCDT for selected patients with highly symptomatic acute IFDVT and low bleeding risk, whereas rapid thrombus removal is not recommended for femoropopliteal DVT.[34,51,52]

The modest clinical benefits observed notwithstanding, these trials provided important insights into the validity of the OVH. First, CDT/PCDT and adjunctive procedures were reasonably effective in initially reducing thrombus volume and restoring venous patency in most patients.[53,54] Second, although CDT/PCDT–treated veins were more likely to be thrombus free on follow-up ultrasound examination at 1 month and beyond, an unexpectedly high proportion of treated patients had noncompressible veins. Given the observed favorable venographic procedure results, this finding suggests that subclinical thrombus re-formation, with or without vein wall fibrosis, may be more frequent than previously appreciated after catheter intervention.[55] Catheter intervention also did not reduce recurrent VTE in any of the studies.[15–17] Third, in ATTRACT, a compressible common femoral vein at 1 month was significantly associated with less frequent PTS, less moderate or severe PTS, and improved venous QOL.[55] In CaVenT, ultrasound patency of the iliofemoral veins was similarly associated with improved clinical status.[56] Fourth, in ATTRACT, the volume of residual thrombus on the venogram on the final procedure day did not correlate with 2-year PTS occurrence; however, in the IFDVT subgroup only, the residual thrombus volume correlated with PTS severity.[55] Last, effects of catheter intervention on valvular reflux were modest: CaVenT (which studied intrathrombus infusion–only CDT without thrombectomy device use) observed a small reduction in deep valve reflux, but ATTRACT did not find any reduction in valvular reflux after PCDT.[55,56] In ATTRACT, femoropopliteal venous reflux was a key factor in development of moderate or severe PTS. It should be noted that these studies were statistically designed to detect a difference in the binary occurrence of PTS, but they were not large enough to provide definitive data on many important secondary outcomes.

These major clinical trials have made it clear that the original formulation of the OVH, although perhaps easy to understand, is greatly oversimplified relative to the scope of pathophysiological factors driving PTS. Therefore, a more comprehensive understanding of PTS development and modulation of other risk factors is warranted.

RE-EXAMINING THE PATHOPHYSIOLOGICAL EVOLUTION OF DVT INTO PTS

The pathophysiology of PTS is complex and yet to be fully elucidated, but venous hypertension arising from venous outflow obstruction and valvular reflux appear to play a central role[1,2] (Figure 2). Inflammation is also thought to be a key driver of PTS, involving a coordinated, thrombus-driven inflammatory response initiated by neutrophils, followed by monocyte/macrophage infiltration.[1–3,57] Inflammatory cells participate in vein wall and vein valve fibrosis, with consequences that include valvular incompetence at the affected DVT site or extending into distal bystander veins, venous stenosis, and recurrent DVT.[1–3,57] Clinical studies have demonstrated that blood inflammatory biomarkers (eg, C-reactive protein, interleukin-6, intercellular adhesion molecule-1) may

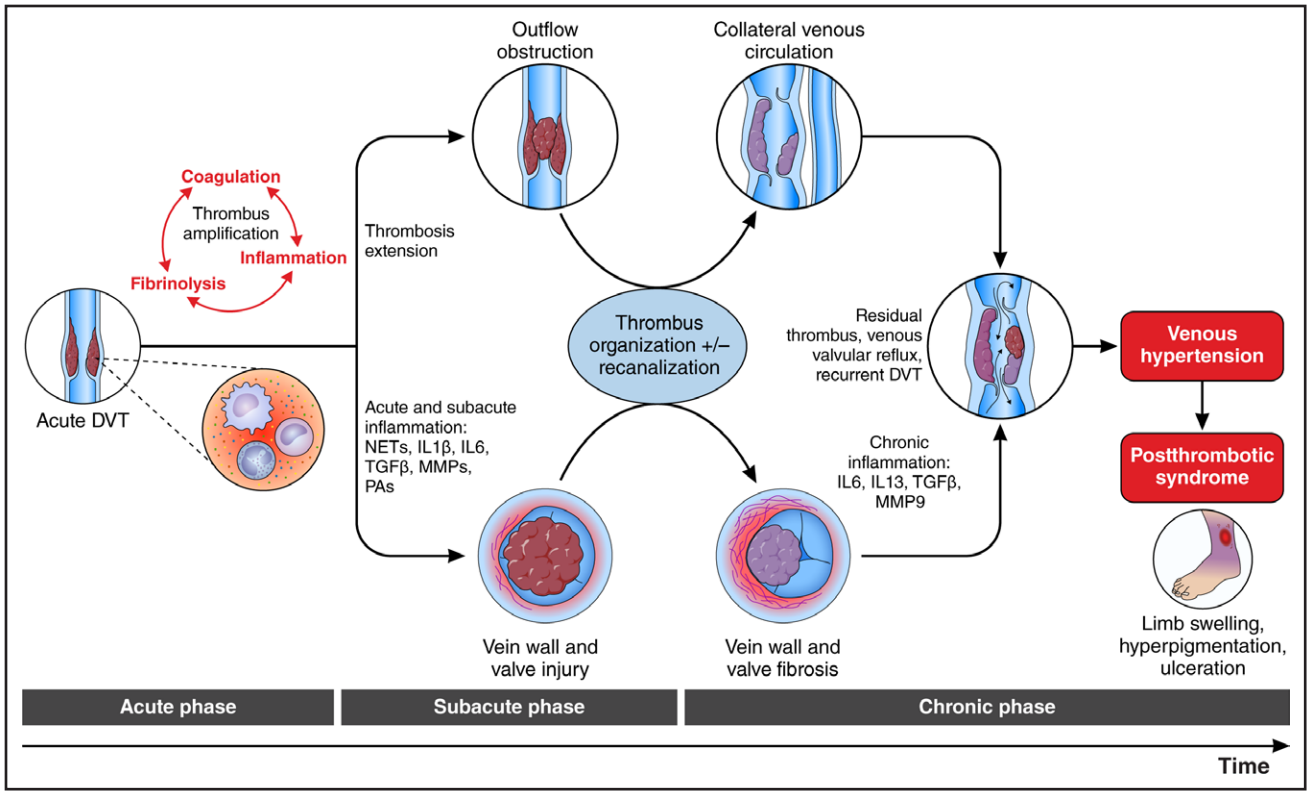

Figure 2. Proposed pathophysiology of postthrombotic syndrome after acute DVT.
DVT indicates deep vein thrombosis; IL, interleukin; MMP, matrix metalloproteinase; NET, neutrophil extracellular trap; PA, plasminogen activator; and TGFβ, transforming growth factor-β.

weakly predict an increased risk of PTS.[1,57–59] In addition, experimental animal studies and preliminary clinical trials indicate that pleiotropic anti-inflammatory medications such as statins, colchicine, and antiselectin could reduce vein wall injury and fibrosis and thus potentially could reduce PTS.[12,60–64] Therefore, anti-inflammatory strategies to reduce PTS may merit further investigation.

Other potentially important factors concerning fibrinolytic capacity, vein wall injury, and PTS development include the time to DVT recanalization and residual blood flow hemodynamics, specifically the duration of thrombus presence and when restoration of blood flow is achieved within the obstructed vein segment.[2,20,21] In contrast to arterial reperfusion, venous reperfusion is rarely clinically urgent because there is an extremely low risk of limb loss. Although fibrinolytic capacity diminishes with thrombus chronicity, fibrinolytic drugs can sometimes lyse venous thrombus out to 10 to 14 days from symptom onset, and adjunctive endovascular methods (ie, balloon angioplasty and stent placement) can restore venous patency even when thrombus cannot be entirely removed.[15–17] For these reasons, in clinical practice, CDT/PCDT is considered appropriate to provide as far out as 14 to 21 days.[34,51] Although currently unsupported for routine use by RCT data or clinical practice guidelines, some large-bore mechanical thrombectomy devices appear to be able to remove intraluminal thrombotic material even beyond 21 days.[65] However, the critical questions related to injury and timing remain: (1) Relative to the patient's symptom course, when do vein wall and valve injury occur, and when do the injury and fibrosis become irreversible? (2) To what extent can vein wall and valve injury be reduced by various clinical therapies? (3) What amount and type of vein wall and valve injury, if any, result from use of specific endovascular tools and strategies?

To explore these questions further, Li and associates[20] examined the time-dependent role of reperfusion in a murine stasis DVT model and in a post hoc exploratory analysis of ATTRACT trial data. Experimentally, the authors found that reperfusion of DVT could prevent murine DVT-induced vein wall fibrosis and inflammation, but only if restoration of blood flow occurred within 4 days of occlusion. Of note, if blood flow was already present by day 4, exogenous fibrinolysis did not further reduce vein wall fibrosis. In their post hoc analysis of the ATTRACT clinical trial data, there was a suggestion for similar findings: Beyond 8 days from symptom onset to randomization, there may have been diminishing long-term PTS benefits of PCDT+anticoagulation compared with anticoagulation alone. The maximal benefit of PCDT on PTS in the ATTRACT trial appeared to occur in patients with DVT symptoms of 4 to 8 days, with no benefit in patients randomized within 0 to 3 days of symptom onset. This observation suggests that some patients with early-stage DVT

have a higher capacity for endogenous fibrinolysis that can lyse acute thrombus in the setting of anticoagulation alone.[20] Biomarkers of coagulation-fibrinolysis (eg, plasma fibrinogen, d-dimer) may further help to identify patients who will not be able to adequately lyse a thrombus via endogenous fibrinolysis.[1,66] Moreover, long-persisting DVT may irreversibly damage the adjacent vein wall and valves, promoting valvular reflux. Thus, an intermediate time frame (eg, days 4–8) since symptom onset may exist during which catheter-directed interventions plus anticoagulant therapy could further prevent or reduce PTS compared with anticoagulation alone. This refined, time-restricted OVH requires prospective clinical testing to determine whether selective catheter-directed interventions based on DVT age can improve PTS outcomes.

IMAGE GUIDANCE TO PERSONALIZE TREATMENT OF ACUTE IFDVT

Optimization of PTS prevention strategies requires comprehensive information on patients' symptom onset, anatomic thrombus location and burden, and bleeding risk.[34,51] Beyond anticoagulant therapy, additional rapid thrombus removal with CDT/PCDT is typically considered for highly selected patients with symptom duration <14 to 21 days.[34,51] After 21 days, thrombi more often harbor organized, collagen-rich material resistant to fibrinolysis or extraction by CDT/PCDT.[15–17] However, given the variability in DVT symptoms and the timing of patient presentation, the patient-derived symptom onset history and conventional DVT imaging methods do not precisely assess the biological age of a DVT or the extent of vein wall injury, making it difficult to deploy time-dependent therapeutic strategies. Accordingly, there is substantial interest in developing new noninvasive imaging methods to objectively assess thrombus age and fibrinolytic responsiveness, the inflammatory status of the thrombus and vein wall (eg, neutrophil, macrophage, fibroblast, protease activity), and additional pathophysiological changes that affect PTS. A comparison of conventional and newer clinical imaging modalities is given in Table 1.[61,67–73]

Venous duplex ultrasound (VDUS) is a real-time, noninvasive, portable, economical imaging modality that reliably assesses thrombus extent, venous patency, hemodynamic parameters, and valvular function. The routine practice of evaluating DVT only with VDUS, however, can miss iliocaval vein thrombus and obstructive lesions in some patients who may require additional cross-sectional imaging approaches or invasive venography.[74,75] Certain sonographic features correlate with an acute DVT (eg, noncompressible vein with central hypoechoicity, often with venous dilatation) or chronic postthrombotic changes (eg, shrunken echogenic vein with visible channels/webs), but many patients have thrombus of mixed or uncertain chronicity that cannot be confidently characterized.[74] A sonographic finding of an "acute" thrombus indicates that it likely formed within the past 14 days, a broad time period that may span multiple phases of the pathobiological processes that dictate PTS development and responsiveness to preventive therapies. On the basis of the pros and cons mentioned previously, the critical questions related to ultrasound remain: (1) Can point-of-care ultrasound be integrated into multidisciplinary team care for patients with IFDVT that may help clinicians make informed decisions quickly such as procedural guidance and monitoring? (2) Can VDUS be optimized to better imaging iliocaval thrombosis and venous patency and how? (3) Can ultrasound elastography or contrast-enhanced ultrasound provide additional information on thrombus chronicity and vein wall injury cost-effectively?

Computed tomography venography and magnetic resonance venography can readily visualize the pelvic veins; show high sensitivity and specificity for DVT diagnosis in limited studies; and can often identify and characterize iliocaval venous thrombus, stenosis, and obstruction in the acute and chronic postthrombotic phases of disease.[76,77] For computed tomography venography and contrast-enhanced magnetic resonance venography to be optimal, imaging must be timed to the arrival of the contrast bolus in the target vein. This can be challenging because of variability in patient size, cardiac output, and flow dynamic changes in the presence of venous obstruction. For patients with implants that are not compatible with magnetic resonance imaging, the artifacts can preclude evaluation of venous structures. Although there are no large clinical studies evaluating the ability of computed tomography venography and magnetic resonance venography parameters to predict PTS development, some studies suggest that cross-sectional imaging can discriminate thrombus chronicity and thereby assist in decisions on the use of adjunctive therapies.[73,76]

For these reasons, many endovascular interventionalists favor obtaining cross-sectional imaging or direct invasive imaging to more accurately assess the status of the target vein planned for intervention. Multiplanar venography can depict the vessel lumen and thereby indirectly provide information on thrombus chronicity and vein wall status from the observed pattern of filling defects.[78] IVUS can directly visualize intraluminal material and vein wall characteristics (eg, echogenicity, thickness, webs/synechiae); however, it is not validated for evaluating thrombus chronicity in acute DVT, and no validated IVUS-based volumetric venous thrombus scoring systems are currently available.[79–81] However, in the setting of established chronic venous disease, the addition of IVUS to multiplanar venography for iliac vein assessment was shown in the prospective multicenter Venogram vs IVUS for Diagnosing Iliac Vein Obstruction trial (NCT02142062) to identify more obstructive lesions; to provide superior characterization of venous stenosis, internal defects, and the vein wall; and to predict response to endovascular therapy.[81] Based on these

Table 1. Summary of Imaging Modalities for Iliofemoral DVT

Modality	Advantage	Disadvantage	Current status
Noninvasive			
Ultrasound			
VDUS	Accessible, no radiation, no renal toxicity, real-time and economical imaging modality; ability to evaluate venous patency and valvular function in extremity veins; potential to evaluate vein wall thickness	Operator dependent; can be limited by bowel and body habitus; low capability in imaging iliocaval lesions (only indirect signs from Doppler flow pattern)	First-line diagnostic modality for suspected acute DVT; with secondary signs suggestive of iliocaval DVT, may consider further advanced imaging
US elastography	Potential ability to assess thrombus age, acute DVT with lower stiffness and lower strain ratio; shear wave elastography is operator independent	Strain elastography is operator dependent and requires external compression; not easy to differentiate thrombus with mixed chronicity; limited literature on venous structure currently	Preclinical animal studies; small sample size, 1-center pilot study; further studies are warranted to validate these findings; not routinely used in vascular imaging
Contrast-enhanced US	Good safety profile of ultrasound microbubbles; potential ability to improve detection of small thrombus; potential ability for poststenting surveillance with ICVO	Expensive; time consuming; specialized equipment and software; additional CEUS may not affect the management of DVT	Preclinical studies; small sample size, single-center pilot study; further studies are warranted to validate these findings; not routinely used in vascular imaging
Computed tomography venography			
	Fairly sensitive and specific in diagnosing ICVO; can identify acute thrombus and gross morphological changes and contribute to poststenting surveillance; in patients with suspected PE, combining indirect CTV with CTPA may negate the need for additional contrast; ability to evaluate venous patency; can visualize surrounding pathology (eg, compressive mass)	Expensive; incremental radiation dose and contrast load; particular to reproductive organs in the pelvis; reliant on timing of contrast arrival to image acquisition; limited resolution for intraluminal defects such as webs; contrast mixing artifacts can mimic thrombus	CTV should not be the first-line diagnostic modality for acute DVT but may be useful when VDUS is inconclusive or when there is suspected ICVO; for patients suspected with ICVO, CTV is useful in the diagnosis, treatment planning, and posttreatment surveillance
Magnetic resonance			
MRV	Fairly sensitive and specific in diagnosing ICVO; potential to differentiate acute, subacute, and chronic thrombi; superior ability to delineate anatomy above inguinal ligament; ability to evaluate venous patency; potential ability to evaluate vein wall thickness and hemodynamics	Expensive; contrast agent may be contraindicated in patients with renal failure; limited use in patients with venous stent due to susceptibility artifacts; limited literature on venous structure; limited resolution for intraluminal defects such as webs	MRV should not be the first-line diagnostic modality for acute DVT but may be useful when VDUS is inconclusive or when there is suspected ICVO; for patients with suspected ICVO, MRV is useful in the diagnosis, treatment planning, and posttreatment surveillance
Magnetic resonance direct thrombus imaging	Potential to differentiate acute, subacute, and chronic thrombi; potential ability to differential ipsilateral recurrent DVT and chronic postthrombotic changes	Expensive; requires specialized software; MRI artifacts can preclude evaluation of venous structure for patients with venous stent	Single-center clinical study; 1 multicenter clinical trial in recurrent DVT; not yet routinely used in vascular MRI imaging protocols
Positron emission tomography	High sensitivity, whole-body imaging; quantitative measurement of DVT inflammation; combination with CT/MRI could enhance anatomical localization and diagnostic accuracy; potential to assess DVT age and recurrent DVT; potential to assess inflammatory status of DVT and predict vein wall scarring and risk of PTS (FDG-PET)	Expensive; limited specificity; radiation exposure; contrast load; lower spatial resolution; timing consuming	Preclinical animal studies; small sample size, single-center clinical studies; further studies are warranted to validate these findings in larger sample size; not routinely used in vascular imaging currently
Invasive			
Multiplanar venography	Historical gold standard in diagnosing DVT; depicts the vessel lumen; indirectly provides information on thrombus chronicity and vein wall status; provides visual assessment of in-line and collateral venous flow; ability to evaluate venous patency and hemodynamics; can be performed through extremity vein injection or image-guided catheter insertion	Invasive; operator dependent; limited by technical factors such as access site edema, contrast load; susceptible to artifacts due to inflow of nonopacified blood and other factors poorly suited to evaluate vein wall architecture and to identify internal defects; 2-dimensional assessment of a 3-dimensional structure	Not routinely used in DVT diagnosis unless endovascular intervention is planned; typically used to guide catheter-directed endovenous interventions
Intravascular ultrasound	Provides superior delineation of intravascular dimensions, venous stenosis (better identification and characterization), and landmarks for venous stenting; can direct visualize intraluminal material and vein wall remodeling characteristics such as echogenicity, thickness, webs/synechiae	Invasive; expensive; operator dependent; limited field of view and tissue penetration	IVUS provides complementary information to venography; guidelines suggest use of IVUS for iliac vein assessment in acute DVT when invasive venography is performed

CEUS indicates contrast-enhanced ultrasound; CT, computed tomography; CTPA, computed tomography pulmonary angiography; CTV, computed tomography venography; DVT, deep vein thrombosis; FDG-PET, fluorodeoxyglucose positron emission tomography; ICVO, iliocaval venous obstruction; IVUS, intravascular ultrasound; MRI, magnetic resonance imaging; MRV, magnetic resonance venography; PE, pulmonary embolism; PTS, postthrombotic syndrome; and VDUS, venous duplex ultrasound.

indirect data and clinical experience, societal guidelines recommend the use of IVUS for iliac vein assessment in patients with acute IFDVT when invasive venography is performed.[34]

Direct visual inspection of thrombus extracted from the venous system has also been used to define chronicity but has important limitations: (1) It requires an invasive procedure and is not available a priori for determining on whom to intervene; (2) extracted thrombus may differ in composition from residual material, and both may be disrupted by the technique of extraction; and (3) the visual assessments of the extracted thrombus may not always be accurate, especially if the thrombus is of mixed chronicity and pathology expertise is not use.

Given the limitations of existing imaging modalities, new imaging approaches that better characterize thrombus chronicity, venous patency, and vein wall biology could inform the optimal timing of therapeutics, including fibrinolytic therapy and catheter-directed interventions. Looking forward, some studies indicate that direct thrombus imaging with magnetic resonance imaging and positron emission tomography can distinguish thrombus age and recurrent DVT in patients.[68,70,82–85] On magnetic resonance imaging, T1 relaxation has been shown to reflect iron processing and to predict susceptibility to fibrinolysis.[86] In animal studies, molecular imaging of fibrin with magnetic resonance or near-infrared fluorescence can identify venous thrombus amenable to fibrinolytic therapies.[21,73] In mice, fluorodeoxyglucose positron emission tomography imaging can identify acute thrombus and thus thrombus age to more precisely diagnose recurrent DVT, image thrombus, and vein wall inflammation, as well as statin-mediated reductions of DVT inflammation and subsequent vein wall scarring.[61,72] In addition, radiomics, the field of extracting and mining quantitative features from radiological images, has emerged as a promising source of noninvasive imaged-based biomarkers that may further advance diagnostics and risk assessment for patients with DVT. Additional studies are needed to further validate these novel approaches to determine whether they can improve prediction of PTS and can be reasonably incorporated into clinical practice in a pragmatic and cost-effective manner.

EMPHASIZING PTS REDUCTION AS A CRITICAL GOAL OF CONTEMPORARY COLLABORATIVE IFDVT CARE

The care of venous thrombosis has improved in recent decades as a result of extensive multispecialty collaboration around hospital-based DVT prevention; patient advocacy to increase layperson education on DVT symptoms, signs, and risk factors; improvements in imaging diagnosis; and improvements in anticoagulant drugs and related monitoring.[1,87] The risk factors for DVT include but are not limited to major surgery or trauma, active cancer, pregnancy, use of hormonal agents such as oral contraceptives, immobility due to chronic disease, hospitalization or acute illness, obesity, inflammation, and long-haul travel.[1,87] These accomplishments have been important also because each case of DVT prevented is one less patient at risk for PTS.

Nevertheless, over many years, statements from multiple societies, including the American Heart Association, have recognized acute IFDVT as a readily identifiable condition that carries a high risk for poor patient outcomes and have urged a holistic view of care that goes beyond anticoagulation management.[33,34,51,88] Despite this long-standing consensus, in most centers, patients with IFDVT continue to be managed similarly to patients with less extensive DVT, and PTS mitigation is not routinely considered a key therapeutic goal. This highlights a pervasive educational gap that urgently needs to be bridged through collaborative action. Additional data are needed before newer therapies that involve risks and costs can be routinely applied. However, even as data collection progresses, patients with IFDVT should be afforded the best chance to avoid PTS and its consequences on the basis of what is currently known, with a priority on their safety. This scientific statement suggests that the following framework will improve IFDVT clinical care and help to expedite enrollment in clinical trials that are evaluating new IFDVT therapies.

First, patients with IFDVT should be labeled as such at the time of DVT diagnosis and should be referred for closer monitoring. For local clinicians and hospitals, this approach means treating the ultrasound finding of common femoral vein thrombus (regardless of whether iliac DVT is present) as a high-risk condition, actively tracking the outcomes of patients with IFDVT, and adopting best care practices, to the extent known, for reducing PTS. For investigators and regulatory agencies who oversee clinical trials of DVT therapies, this consideration means routinely requiring rigorous, unbiased, and well-validated clinical assessments for PTS and separate reporting of outcomes in patients with IFDVT.

Second, an integrated multidisciplinary care model should be applied for patients with IFDVT, ideally incorporating a primary care physician and other experts who can advise on the patient's antithrombotic care, physical rehabilitation, lifestyle modifications, and catheter-based interventions.[89–91] Effective communication should occur between these clinicians and the patient. The patient's symptoms and functional limitations should be actively questioned and correlated to evolving sonographic findings such as dynamic changes of thrombus extent, venous patency, and valvular reflux. A 2-stage multidisciplinary approach for patients with acute IFDVT may be helpful in ensuring that symptoms and PTS risks are addressed during follow-up (Figure 3).

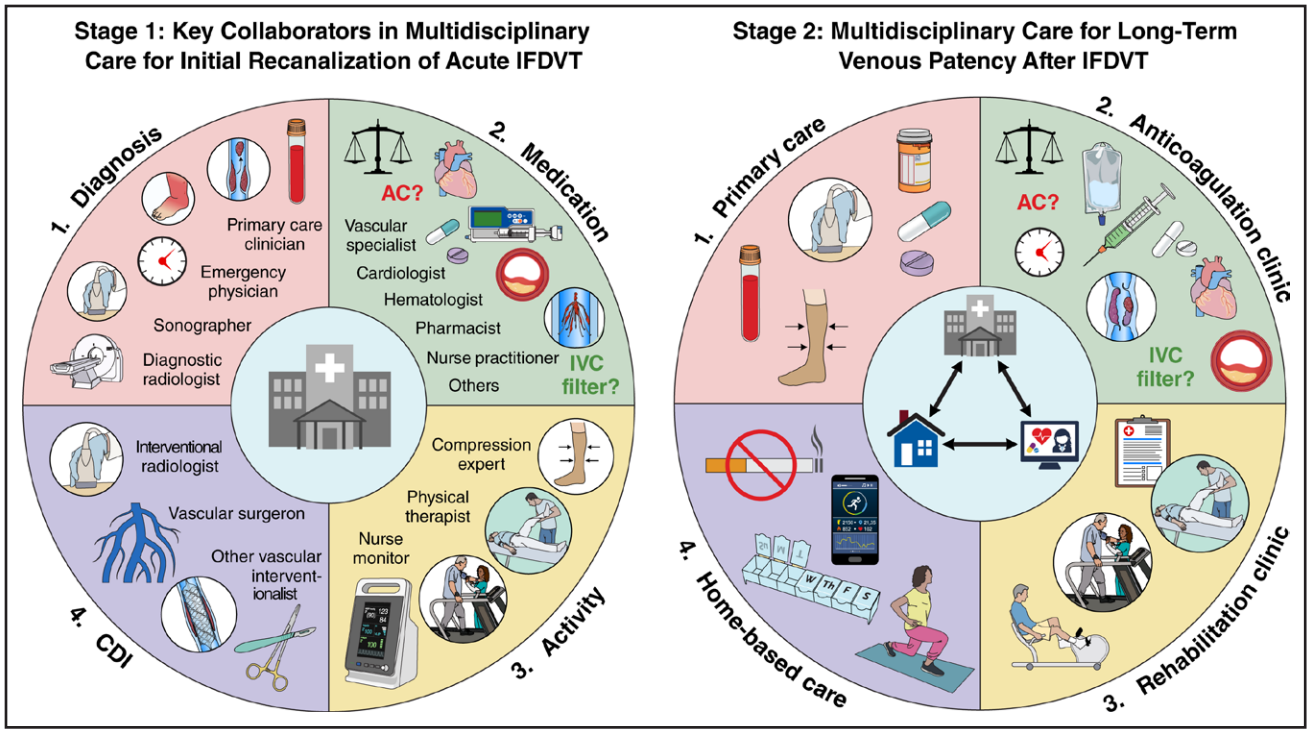

Figure 3. Proposed 2-stage patient-centered multidisciplinary care to reduce PTS after IFDVT.
A, Key collaborators in initial multidisciplinary team (MDT) to ensure excellent initial iliofemoral deep vein thrombosis (IFDVT) care that encompasses rapid diagnosis, timely and effective anticoagulation (AC), symptom reduction that permits return to normal activity, and risk stratification for the appropriateness of additional interventions to reduce postthrombotic syndrome (PTS). **B**, Stage 2 MDT to maintain a focus on PTS mitigation through quality follow-up, assessment of symptoms and functional status, reduction of venous thromboembolism recurrence, and consideration of additional interventions for selected patients. Potential referrals to anticoagulation clinic, rehabilitation clinic, and other specialists should be considered according to the patient's condition. Telehealth tools may facilitate the development of home-based care and enhance the equitable access to care. CDI indicates catheter-directed intervention; and IVC, inferior vena cava.

Stage 1: Short-Term Multidisciplinary Management of Acute IFDVT

Patients with acute IFDVT should be carefully evaluated by their primary care clinicians for symptoms and physical examination signs that may suggest symptomatic PE or phlegmasia cerulea dolens. Close monitoring, risk stratification, and (when indicated) rapid referral to a specialist for consideration of emergency catheter-directed or surgical interventions should be prompted in the presence of critical conditions such as hemodynamically unstable PE or phlegmasia cerulea dolens.[34,51,52] Consideration of intervention may also have urgency in rare instances when extensive iliocaval thrombus extends into the renal or hepatic veins or poses an usually high risk of fatal PE.[34,51,52]

Rapid achievement of therapeutic anticoagulation is the cornerstone of effective therapy for IFDVT.[52] The care plan for each patient needs to be individualized and will depend on limb symptom status, comorbidities, bleeding risks, and the potential cause(s) of the IFDVT. For example, patients with cancer may have high propensity to bleed or to be thrombocytopenic, which may influence the anticoagulation strategy. Consultation of relevant specialists (eg, hematology, vascular medicine, pharmacy) may be beneficial in specific situations such as suspected heparin-induced thrombocytopenia, suspected antiphospholipid syndrome, moderate to severe kidney disease, or active bleeding or during periprocedural settings, each of which can influence the needed antithrombotic therapy strategy. If anticoagulation is contraindicated or fails to prevent PE or major thrombus extension, consultation of endovascular specialists for placement (and timely retrieval when the PE risk has subsided) of an inferior cava filter may be indicated. Subject to local resources and expertise, a hospital-based dedicated thrombosis service or collaborative structures similar to the pulmonary embolism response team concept may be entertained. A DVT-focused multispecialty team may only rarely need to meet emergently in stage 1. Its composition and timing can reflect the lower medical acuity of most patients with DVT (compared with intermediate-risk or high-risk PE), as well as local resources and expertise.

Management of limb edema and pain can be challenging in patients with acute IFDVT. Limb compression and early ambulation should be started after anticoagulation is begun, ideally with supervision from a physical therapist or nurse practitioner when the patient's mobilization is difficult.[52,92,93] If the limb is too tender in the acute setting,

elastic or nonelastic bandages can be used before ECS fitting. From a pathophysiological point of view, compression initiated early may be more effective in preventing PTS because it could augment calf pump function and venous blood flow and thereby improve thrombus resolution and reduce vein wall fibrosis.[9,93] Mobility should be encouraged in most patients, but when the patient is resting, lower-extremity elevation may also be helpful in reducing edema and acute symptoms.

Changes in patient symptoms should be closely monitored as a prioritized goal of care. Use of standardized tools to measure DVT symptoms and PTS (eg, Villalta scale and Venous Clinical Severity Score) is strongly encouraged to track symptom severity over time. If the patient does not improve over the subsequent days, timely VDUS should be considered to re-evaluate thrombus extent and venous patency. If symptoms worsen or continue at moderate to severe intensity, especially if the thrombus is not resolving on VDUS, selected patients with IFDVT (low risk of bleeding, high chance of technical success) can be referred to interventionalists to consider whether catheter-directed intervention is indicated to reduce DVT symptoms and PTS severity.[34,51,52] For patients who undergo a procedure, the perioperative anticoagulation care plan should be proactively addressed and may vary according to the characteristics of the individual patient and the planned treatment.

Stage 2: Long-Term Patient-Centered Management After IFDVT

The need for extended anticoagulation for >3 months is based on the projected or ongoing risks for VTE recurrence balanced with the risks of bleeding, but beyond those, extended anticoagulation is usually not recommended for the primary purpose of PTS prevention.[52] The efficacy of different types of anticoagulants on PTS prevention may be mediated by the differences in the capacity of recanalization, reduction in recurrent VTE, anti-inflammatory properties, and stability of the anticoagulation effect.[94–100] However, at present, there are no specific recommendations on the type of anticoagulant that is best for PTS prevention after DVT. Small comparative studies and a meta-analysis suggest that rivaroxaban may offer better PTS prevention efficacy than vitamin K antagonists[96–98] and that low-molecular-weight heparin with anti-inflammatory properties may offer better efficacy for PTS prevention than vitamin K antagonists and direct oral anticoagulants.[94,95,99] An ongoing pilot study is comparing low-molecular-weight heparin with direct oral anticoagulant for PTS prevention in patients with acute IFDVT.[100] For patients with IFDVT after catheter interventions, there are no rigorous prospective studies comparing antithrombotic strategies. Currently, it remains inconclusive which type of anticoagulant can be the optimal choice and what the role and efficacy of antiplatelets are in initial and maintenance therapy, respectively.[101,102] Active collaboration between endovascular physicians and thrombosis specialists should increase the ability to effectively individualize antithrombotic care in these populations.

Besides nonmodifiable risk factors (eg, DVT location, sex, race), an important aspect to consider in reducing PTS is managing modifiable risk factors such as inflammation, obesity, and smoking beyond optimal anticoagulation.[1,103] Elevated levels of inflammatory biomarkers (eg, C-reactive protein >5 mg/L; odds ratio, 8.0 [95% CI, 2.4–26.4]; interleukin-6 above the median value of controls; odds ratio, 1.66 [95% CI, 1.05–2.62]) are significantly associated with PTS incidence.[1,2] Emerging studies indicate that pleiotropic anti-inflammatory medications such as statins and colchicine may modulate vein wall injury and fibrosis.[3,10,11,61,62] Obesity (body mass index ≥30 kg/m^2; odds ratio, 2.63 [95% CI, 1.47–4.70]) is another modifiable risk factor associated with PTS.[1] Although weight loss and exercise are encouraged to alleviate PTS symptoms, the roles of specific weight management interventions have not been evaluated for the reduction of PTS.[3,5] Further research on the role of antithrombotics, anti-inflammatory interventions, weight management, and supervised exercise training after IFDVT to prevent or reduce PTS is warranted. In addition, including PTS measures and patient-reported outcome measures (including assessments of QOL) in outcome evaluations for future trials of DVT therapies (not limited to endovascular treatments) is also warranted. Selected clinical trials that aim to address potential measures that may prevent/reduce PTS are summarized in Table 2.

During follow-up, ECS and other compression therapies may be useful in reducing limb edema and other symptoms. Their effectiveness and tolerability should be regularly questioned and adjusted (eg, compression level, stockings length, frequency and duration of use, donning aids, adherence) at follow-up visits, to increase the likelihood of consistent compliance and to achieve optimal results for symptom reduction.[9,104–106] Patient-centered multidisciplinary care and quality follow-up are warranted to maintain venous health in the long term through supervised home-based care.

ENSURING CARE DELIVERY AND RESEARCH IMPLEMENTED EFFICIENTLY, SAFELY, AND EQUITABLY

There are systematic health disparities in morbidity, mortality, and other measures of well-being in vascular diseases. Although some studies have investigated sex- and race-based disparities in DVT incidence and recurrence, the evidence level is moderate, and sparse studies have aimed to address biology-, geography-, and social determinants of health–based disparities that may affect venous pathophysiology, response to therapy, incidence and

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Table 2. Selected Clinical Studies With Relevance to PTS Reduction

Study (No.)	Study design	Main outcome measures	Main aims
Risk factors			
DVT-Burden (NCT06385353)	Multicenter prospective cohort study; single group assignment; open label; duration of 6 mo; 400 participants diagnosed as first episode of unprovoked DVT of lower limbs	Primary: presence of PTS; baseline thrombus burden by VDUS Secondary: presence of PTS adjusted with risk factors; time to thrombus resolution Other: QOL, coagulation and fibrinolysis markers	Assess baseline DVT burden and other prognostic factors for predicting PTS; identify patients at high risk of developing PTS for better prevention and therapeutic strategy to reduce incidence and severity of PTS
RIETE (NCT02832245)	Multicenter registry; duration of 3 y; 120 000 participants with VTE	Recurrent VTE, PTS, bleeding, mortality	Improve knowledge on the natural history of VTE, particularly in subgroups of patients usually not recruited in RCTs; create predictive scores to better identify those at high risk of related complications
RRT VTE (NCT03881345)	Multicenter registry; duration of 12 mo; 5000 participants with VTE	Primary: venous patency Secondary: PTS, QOL	Evaluate venous patency and PTS for patients with VTE treated by means of antithrombotic therapy, thrombolysis, open surgery, endovenous deobstruction, and stenting
Imaging			
GrAVISPT (NCT06451484)	Single-center retrospective observational study; baseline imaging; 50 participants with chronic venous thrombosis	Primary: baseline grade of vein severity on phleboscanner Secondary: interobserver reproducibility on MRI, reproducibility between MRI and phleboscan	Improve the diagnosis of chronic DVT before venous recanalization procedure; confirm whether MRI scores are comparable to CT scores
Novel PET/CT and Treatment Strategies to Reduce PTS Following DVT (NCT03195777)	Single-center, prospective observational study, open label, assessor blinded; duration of 24 mo; 80 participants with acute proximal DVT	Primary: incidence of PTS at any time during follow-up Secondary: PTS severity during follow-up	Develop strategies that will improve outcomes for patients with DVT; develop FDG-PET inflammation imaging that can better predict risk of developing PTS
Medical therapy			
CONQUER-DVT Pilot (NCT06440694)	Single-center RCT; parallel assignment (colchicine+AC vs AC); quadruple masking; phase 3; duration of 12 mo; 150 participants with acute proximal DVT	Primary: recruitment rate, incidence of PTS Secondary: eligibility and adherence rate; consent rate, retention rate, severity of PTS; recurrent VTE; bleeding; QOL	Assess the feasibility of whether low-dose colchicine could further reduce the risk of PTS on the top of AC
MUFFIN-PTS (NCT03833024)	Multicenter RCT; parallel assignment (MPFF vs usual treatment); triple masking; phase 3; duration of 6 mo; 88 participants with PTS	Primary: changes in PTS Secondary: severity of PTS, QOL, Villalta score, venous ulcer	Evaluate the effectiveness and safety of MPFF compared with placebo for the treatment of PTS
SAVER (NCT04319627)	Multicenter RCT, parallel assignment (rosuvastatin+AC vs AC), quadruple masking; phase 3; duration of 60 mo; 2700 participants with proximal DVT±PE (segmental or greater) diagnosed <30 d	Primary: symptomatic recurrent major VTE Secondary: PTS incidence, nonmajor VTE, major bleeding	Determine whether generic rosuvastatin reduces the risk of recurrent VTE; explore whether rosuvastatin reduces incidence of PTS
SIRIUS (NCT06149520)	Multicenter RCT, parallel assignment (anti-α2AP antibody+AC vs AC), phase 2; duration of 90 d; 255 participants with acute symptomatic proximal DVT	Primary: AUC (6 h–30 d) ratio to baseline of clot burden, bleeding Secondary: ratio to baseline of clot burden up to 90 d, change in leg pain severity, recurrent VTE	Determine the efficacy and safety of this novel fibrinolytics in dissolving blood clots for proximal DVT
TILE Pilot (NCT04794569)	Multicenter RCT; parallel assignment (LMWH+rivaroxaban vs rivaroxaban); assessor blinded; phase 4; duration of 6 mo; 60 participants with acute iliofemoral DVT	Primary: PTS; eligible, recruited and adherence rate Secondary: severity of PTS, QOL, recurrent VTE, SAEs	Determine the sample size and assess feasibility for a larger study; determine whether LMWH targeting the initial acute inflammatory phase could provide additional benefits on PTS reduction
Anticoagulant Plus Antiplatelet Therapy Follow Iliac Vein Stenting (NCT04694248)	Multicenter prospective cohort study; single group assignment (rivaroxaban+aspirin), open label; duration of 12 mo; 172 participants with iliac vein stenting	Primary: venous patency by VDUS and major bleeding event at 12 mo Secondary: venous patency, bleeding events, rate and severity of PTS, recurrent DVT at 3, 6, 12 mo	Evaluate the efficacy and safety of combination of anticoagulant and antiplatelet therapy on venous patency at 12 mo after iliac vein stenting

(*Continued*)

Table 2. Continued

Study (No.)	Study design	Main outcome measures	Main aims
Compression therapy			
CELEST-LT (NCT06046807)	Multicenter prospective cohort study; parallel assignment (25–mm Hg ECS vs 35–mm Hg ECS); duration of 7 y; 288 participants with proximal DVT enrolled in the CELEST RCT	Primary: proportion of patients with moderate to severe PTS Secondary: predictors of moderate to severe PTS, impact of initial ECS strength/type on the development of moderate-severe PTS, QOL	Assess the very-long-term risk of PTS in patients enrolled in the CELEST RCT; improve the knowledge of the epidemiology of burdensome PTS; assess the impact of different initial ECS strengths on the very-long-term risk of PTS
Non-Elastic Compression Garment Therapy Versus Control for DVT (NCT03368313)	Multicenter Bayesian randomized trial; parallel assignment (high-pressure nonelastic compression vs no compression); single masking; duration of 12 mo; 120 participants with acute proximal DVT	Primary: change in pain level and edema after acute DVT Secondary: incidence and severity of PTS, QOL, physical activity	Determine whether nonelastic compression garment could improve PTS outcomes for patients with acute DVT
Physical therapy			
SevERe-PTS Pilot (NCT05744843)	1-center RCT; parallel assignment (supervised exercise treatment vs venous stent vs healthy volunteers); open label; duration of 6 mo; 54 participants with symptomatic chronic venous disease	Primary: Villalta score Secondary: Vo_2max, 6-min walk test, calf ejection fraction, QOL Others: deep venous flow velocity, maximal calf isometric contract strength	Determine the sample size and assess feasibility for a larger study; determine the efficacy of exercise therapy in patients with PTS; confirm what type of exercise is useful in patients with PTS
Endovascular therapy			
BEST (NCT05622500)	Multicenter RCT; parallel assignment (endovenous therapy vs standard therapy) for chronic proximal deep venous disease; double masking; duration of 12 mo; 328 participants with chronic proximal deep venous disease	Primary: VCSS score at 6 mo Secondary: reintervention, stent patency, cost-effectiveness, QOL, Villalta score, Ginsberg score, venous ulceration, walking distance	Confirm the efficacy of optimal endovenous treatment in addition to standard therapy (compression±AC)
C-TRACT (NCT03250247)	Multicenter RCT; parallel assignment (endovascular therapy vs standard therapy); phase 3; open label; single masking; duration of 24 mo; 250 participants with chronic venous disease	Primary: PTS severity over 6-mo follow-up	Determine whether the use of image-guided, endovascular therapy is an effective strategy to reduce PTS severity and to improve QOL in patients with established disabling iliac-obstructive PTS
DEXTERITY-AFP (NCT04862468)	Multicenter RCT; parallel assignment (perivascular dexamethasone vs sham); quadruple masking; phase 2; duration of 6 mo; 80 participants with acute proximal DVT	Primary: rate of primary patency; rate of freedom from major adverse events	Confirm whether local anti-inflammation could help prevent rethrombosis and improvement in symptoms for up to 24 mo after the initial DVT recanalization procedure
DEFIANCE (NCT05701917)	Multicenter RCT; parallel assignment (MT+AC vs AC); open label; duration of 6 mo; 300 participants with IFDVT	Primary: assessment win ratio including PTS severity, occurrence of treatment failure or therapy escalation Secondary: assessment win ratio including vessel compressibility assessed by VDUS, assessment of pain and edema	Evaluate the efficacy and safety of MT in addition to AC in patients with IFDVT
PMT-DVT (NCT06472518)	Multicenter RCT; parallel assignment (PMT+DOAC vs DOAC); open label; phase 4; duration of 60 mo; 228 participants with acute proximal DVT	Primary: cost-utility analysis at 30 mo Secondary: Villalta score ≥10, Villalta score ≥15; major bleeding, venous claudication, QOL, net financial impact over 60 mo	Evaluate medico-economic efficiency of PMT for acute IFDVT; determine the efficacy of PMT on acute symptom change, moderate to severe PTS, QOL

AC indicates anticoagulation; AUC, area under the curve; BEST, Best Endovenous Treatment, Including Stenting, Versus Non-Endovenous Treatment in Chronic Proximal Deep Venous Disease; C-TRACT, Chronic Venous Thrombosis: Relief With Adjunctive Catheter-Directed Therapy; CELEST-LT, Long-Term Post Thrombotic syndrome Assessment; CONQUER-DVT, Colchicine to Quench the Inflammatory Response After Deep Vein Thrombosis; CT, computed tomography; DEFIANCE, RCT of ClotTriever System Versus Anticoagulation In Deep Vein Thrombosis; DEXTERITY-AFP, Perivenous Dexamethasone Therapy: Examining Reduction of Inflammation After Thrombus Removal to Yield Benefit in Acute Femoropopliteal DVT; DOAC, direct oral anticoagulation; DVT, deep vein thrombosis; DVT-Burden, DVT Burden and the Risk of Post-Thrombotic Syndrome; ECS, elastic compression stockings; FDG, fluorodeoxyglucose; GrAVISPT, Grade Analysis of Veins by MRI and CT in Post-Thrombotic Syndrome; IFDVT, iliofemoral deep vein thrombosis; LMWH, low-molecular-weight heparin; MPFF, micronized purified flavonoid fraction; MRI, magnetic resonance imaging; MT, mechanical thrombectomy; MUFFIN-PTS, Micronized Purified Flavonoid Fraction for the Treatment of Post-Thrombotic Syndrome; PE, pulmonary embolism; PET, positron emission tomography; PMT; pharmcomechanical thrombectomy; PMT-DVT, Pharmaco Mechanical Thrombolysis Associated With Anticoagulation Compared With Anticoagulation in the Acute Phase of Very Symptomatic Proximal Venous Thrombosis of the Lower Limbs; PTS, postthrombotic syndrome; QOL, quality of life; RCT, randomized controlled trial; RIETE, Computerized Registry of Patients With Venous Thromboembolism; RRT DVT, Ongoing Registry of Treatment of Venous Thromboembolism; SAE, serious adverse event; SAVER, Statins for Venous Event Reduction in Patients With Venous Thromboembolism; SevERe-PTS, Structured Exercise Versus Endovascular Reconstruction in Post Thrombotic Syndrome; SIRIUS, A Study to Learn More About How Well BAY3018250 Works and How Safe It Is for People With Proximal Deep Vein Thrombosis; TILE, Tinzaparin Lead-In to Prevent the Post-Thrombotic Syndrome; VCSS, Venous Clinical Severity Score; VDUS, venous duplex ultrasound; and VTE, venous thromboembolism.

severity of PTS, and QOL. Studies indicate that females have a higher risk of DVT during pregnancy and estrogen therapy and in postmenopausal status and that males are likely to have higher risk for unprovoked DVT, proximal DVT, and recurrent DVT, although there is no consistent association between sex and PTS.[1,87,107–110] Randomized trials did not find sex-based differences in the effects of CDT/PCDT, except that in 1 trial, females experienced slightly greater thrombus removal but without differences in PTS rates and QOL compared with males with intervention.[15–17,47] Black people appear to have the highest rates of VTE incidence and hospitalization, followed by White individuals and then Hispanic people and Asian/Pacific Islander individuals.[111–113] Black patients are less likely to receive full-course anticoagulation and are more likely to receive an inferior vena cava filter compared with their White counterparts.[114,115] In addition, the incidence of recurrent VTE after idiopathic DVT seems to be highest in Black males, and an exploratory study of ATTRACT trial indicates that self-reported race may affect the Villalta Scale score.[111,116] Health disparities have also been observed in structurally disadvantaged populations such as the elderly, rural residents, individuals with low socioeconomic status, and uninsured patients, who have less access to care service and poorer health-related outcomes.[113,117,118] Explorations and solutions for these barriers are urgently needed, from DVT prevention to PTS management.

Integrating novel technologies such as telehealth and artificial intelligence may facilitate care delivery and research implemented efficiently, safely, and equitably. Telehealth (eg, mobile health, remote patient monitoring, and virtual check-ins) may have a role when in-person follow-up cannot be easily achieved. Data suggest that telehealth management of oral anticoagulation is safe and effective in improving anticoagulation quality with no differences seen in subsequent major bleeding or mortality.[119] This type of care may further improve the tracking of limb symptoms in patients with IFDVT, particularly when symptoms are ongoing or new. Telehealth also has the potential to facilitate supervised home-based exercise, medication adherence, and ECS application to ensure that these tasks are properly and safely performed.[119,120] Artificial intelligence is increasingly being explored and probably could enhance patient health care and research across various settings.[121] Machine learning with big data (eg, genomics, proteomics, radiomics) has potential in identifying pathways and biomarkers that can assist risk stratification and PTS mitigation strategies. Although these novel technologies seem promising and have transformative potential to revolutionize health care, experience with them is limited, and mechanisms to ensure their safety and effectiveness remain underdeveloped.[122–125] Validation of technology-based ecological momentary assessment strategies could help in conceiving early intervention strategies to mitigate PTS.

REFINING THE OVH: PRIORITY RESEARCH QUESTIONS

Since the OVH was proposed several decades ago, clinical trials and basic science studies have provided new insights that now motivate a reappraisal of this conceptual paradigm. With these studies now in the rearview mirror, several issues have become clearer. First, IFDVT is a condition that carries a higher risk for PTS and recurrent DVT than less extensive DVT, despite the use of standard anticoagulation and compression therapy.[1,18,19,33] Clinical trials of DVT treatments should be designed to routinely report on IFDVT outcomes and can even be designed specifically for patients with IFDVT. Second, in the vast majority of affected patients, the diagnosis of IFDVT is apparent from the initial VDUS because the superior extent of the common femoral vein is routinely examined in well-validated VDUS protocols.[67,74] Local pathways of care for patients with IFDVT should be updated to ensure routine identification, closer monitoring, and earlier anticoagulation and referral to specialists in thrombosis and endovascular procedures when appropriate. In modern practice, this approach may be achieved through a combination of automated (eg, electronic alerts) and human (eg, dedicated thrombosis coordinator/service) means. Third, initially regaining an "open vein" is only one part of the overall equation in improving the long-term health of a patient with DVT through the prevention/reduction of PTS.[1–3,57] A better understanding of other mechanisms that contribute to PTS after DVT remains urgently needed, involving pathobiological mechanisms, timing strategy for standard therapies (eg, anticoagulation, compression), and adjunctive catheter-directed interventions (eg, CDT/PCDT, mechanical thrombectomy) based on symptom duration. Fourth, for patients with acute IFDVT who undergo catheter interventions, merely achieving initial recanalization is not likely to be sufficient. Rather, durable achievement of long-term venous patency will usually be needed to expect more freedom from PTS manifestations and thus may require ongoing surveillance and time-sensitive interventions with existing and novel approaches. Fifth, with regard to PTS severity, restoration of patency in the iliac and common femoral veins is likely to be more impactful than recanalization of the femoral and popliteal veins.[18,19] Looking forward, to further refine the OVH and to promote patient-centered personalized care, several priority research areas merit further investigation (Figure 4).

Questions and unmet needs that relate to the initial recanalization with rapid thrombus removal (eg, systemic fibrinolysis, CDT/PCDT, mechanical thrombectomy, surgical thrombectomy) include the following: (1) Develop animal models that could mimic pathophysiological changes of human DVT resolution (eg, thrombus organization, vein wall remodeling, valvular reflux) and PTS signs (eg, limb swelling, hyperpigmentation, ulceration) at different

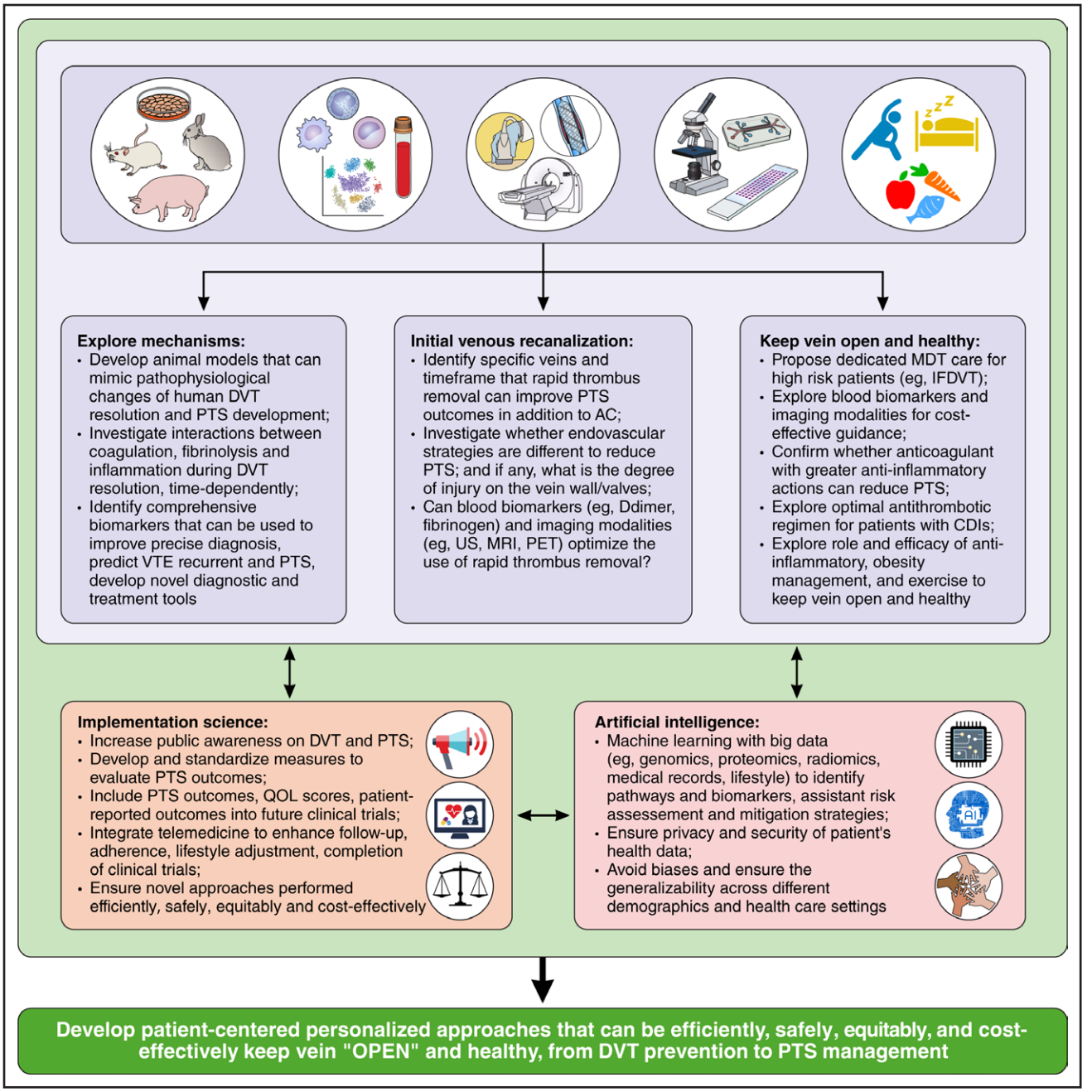

Figure 4. Open vein hypothesis, from "open the vein" to "keep vein open and healthy": priority research areas and questions. Considerations for priority research areas and questions that aim to develop patient-centered personalized approaches to keep the vein open and healthy, from deep vein thrombus (DVT) prevention to postthrombotic syndrome (PTS) management. AC indicates anticoagulation; CDI, catheter-directed intervention; IFDVT, iliofemoral deep vein thrombosis; MDT, multidisciplinary team; MRI, magnetic resonance imaging; PET, positron emission tomography; QOL, quality of life; US, ultrasound; and VTE, venous thromboembolism.

anatomic locations. (2) Continue to improve PTS outcome measures in parallel with the growing insight into the diversity of PTS phenotypes, and routinely include PTS measures and patient-reported outcome measures in therapeutic DVT trials (not just for endovascular interventions). (3) Are there differences among endovascular devices/strategies in thrombus removal efficacy and in the degree to which they exert biological effects on vein wall, valves, blood biomarkers, and surrounding tissues that potentially undermine the benefits of thrombus removal and patency restoration? (4) Is there an optimal time window for rapid thrombus removal, and does that depend on the treatment method? (5) Can imaging-based methods that measure thrombus burden, DVT biological age, and venous flow characteristics further inform the optimal use of rapid thrombus removal on top of conventional therapies? (6) What other VTE risk factors (eg, inflammatory status, obesity, smoking) and cardiovascular

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determinants influence the PTS outcomes of rapid thrombus removal? (7) Are there additional immune or vein wall cellular processes that could be targeted to attenuate vein wall injury and limit PTS development?

Beyond methods to initially clear thrombus and improve venous flow, further questions that relate to the maintenance of long-term venous patency and health to reduce PTS may include the following: (1) With advances in omics platforms (eg, genomics, proteomics, radiomics) and artificial intelligence, is there a differential study that may identify pathways, biomarkers, and scores that may predict thrombus clearance, PTS occurrence and severity, and the effectiveness of PTS mitigation strategies? (2) When does DVT-induced vein wall and vein valve inflammation–driven injury become irreversible, and how can DVT-induced inflammation be monitored in patients to reduce the vulnerability of the adjacent vein wall/valve to fibrosis and eventual reflux? (3) Is the use of anticoagulants with greater anti-inflammatory actions or the use of adjunctive anti-inflammatory therapy, especially in the initial treatment phase, more likely to improve PTS outcomes? (4) What is the optimal anticoagulant and antiplatelet regimen for patients with IFDVT who have undergone an endovascular intervention? (5) Does duplex ultrasound suffice for thrombus burden, blood flow, and valvular function surveillance in the iliofemoral veins? (6) Can imaging modalities (eg, ultrasound, magnetic resonance, positron emission tomography, and near-infrared spectroscopy) that precisely assess components, chronicity, and inflammatory status of thrombus and injured vein wall/valve have predictive value for pathophysiological patterns of PTS development and selection of therapies? (7) Can telehealth and mobile technology facilitate equitable access to patient-centered care, improve PTS outcomes, and speed the completion of relevant clinical studies? (8) How can artificial intelligence and implementation science be integrated to assistant patient-centered care to maintain venous patency and health in efficient, safe, equitable and cost-effective ways, from DVT prevention to PTS management?

SUMMARY

DVT and its burdensome sequelae of PTS are global public health issues that are incompletely understood and underrecognized by many health care professionals. This scientific statement focuses on reducing PTS after lower-extremity DVT, provides an updated understanding of the OVH, proposes a model for state-of-the-art multidisciplinary care for patients with IFDVT, and highlights priority research areas based on basic science, translational research, and clinical practice. Further investigation along these lines will inform efforts to innovate new diagnostic and therapeutic approaches to reduce PTS. Diverse health care clinicians, researchers, organizations, government agencies, communities, industries, and patients can collaborate to increase public awareness of thrombosis, to improve existing approaches to prevent DVT, and to improve the understanding and patient-centered management of DVT and PTS.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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*Modest.

†Significant.

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