ASK THE EXPERTS

If a Government Health Oversight Agency Offered You Full Funding for a Superficial Venous Trial, What Would You Study and Why?

Leading venous practitioners outline the trials that they believe are most urgently needed.

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Disclosures: None.

Superficial venous disease is highly prevalent, negatively affects patients, and is responsible for a significant expenditure of the annual health care budget. Much has been done with respect to assessing different types of intervention, but we still know little about the pathophysiology of the disease and how to predict and act upon factors such as disease progression and disease recurrence. Although approaches to the management of superficial venous disease are applicable to the majority of patients, the way individuals will respond to intervention can be variable; therefore, there is a need to develop more personalized approaches to the management of this condition. Biomarker discovery via basic science research can help provide a means to explore this in more detail, as previous pilot data have shown important findings with respect to molecules of relevance in chronic venous disease.[1,2]

I would set up a large, longitudinal, multicenter, observational study recruiting patients with manifestations of superficial venous insufficiency (any clinical, etiology, anatomic, and pathophysiology [CEAP] stage), with assessment at baseline and follow up at 1, 3, 5, and 10 years. At each stage, clinical examination, quality-of-life assessment, venous duplex ultrasound, and biofluid (serum, urine, and, in C6 patients, ulcer fluid) sampling would be performed. The aim would be to explore patterns of disease progression and correlate these to molecular signatures of relevance with both metabonomic and proteomic assays. Patients undergoing superficial venous intervention would be included to investigate patterns of disease recurrence and whether specific individuals can be identified based on their biology.

The findings of this study would provide a realistic assessment of candidate molecules that can be explored for the development of quick, point-of-care tests to better stratify patients with superficial venous disease and personalize treatment and follow-up in the future.

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Disclosures: None.

Superficial venous disease is the most common pathology associated with venous disease and affects 25% to 40% of adults. Its high prevalence warrants a critical study of indications for treatment. Although we have minimally invasive thermal and nonthermal ablation techniques that can be easily learned, the indications for treatment need clarification to achieve more appropriate application.

Current indications for ablation include the use of a reflux time of > 0.5 seconds, and for those with axial reflux (above and below the knee), it is the standard of care to treat the saphenous vein. However, current guidelines describing indications for treatment do not address extent of reflux. This leads to potential ablation of the entire normal saphenous vein in the presence of a short segment of disease that could be managed with lesser techniques.

To address this need, we could design a randomized controlled trial of saphenous vein reflux with short subsegmental disease comparing two treatments: ablation of the saphenous vein plus treatment of tributaries versus no ablation and treatment of only the affected tributaries leading to symptoms/signs. This may be similar to the ambulatory selective varicose vein ablation under local anesthesia technique (ASVAL) and the ambulatory conservative hemodynamic management of varicose vein technique (CHIVA) described in the literature, but it would not require the details that are unique to these other therapies.

The findings would help us determine whether those with reflux of > 0.5 seconds and subsegmental disease would benefit from a lesser, simpler therapy for tributaries alone or require elimination of the entire saphenous segment. By better clarifying the indications for ablation, unnecessary procedures may be avoided.

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Superficial venous disease is by far the most frequent and thus the most expensive venous problem in industrialized nations, involving a quarter of that entire population. Although treatment has become much simpler and less risky with the introduction of endovenous methods in this millennium, the majority of patients remain untreated until there are symptomatic, large varices, or even tissue damage. The solution for fighting this entity of disease is to determine its origins and establish effective prevention and reasonable early stage therapy.

My study suggestion is related to high-resolution ultrasound analysis (eg, 16–23 MHz) of superficial vein valves. Vein damage is based on valve damage. The three-part study would be related to brand-new discoveries on the three primary mechanisms of vein insufficiency. First, recent studies in children using high-resolution ultrasound systems (16–23 MHz) revealed a surprisingly high incidence of congenital valve lesions (34%–47% in 6- to 8-year-old patients).[1] These lesions are definitely the first to occur in one's life, and they clearly set a primary pattern of the disease. Therefore, the first part of the study I would initiate would be the verification of these results in large, multiethnic populations, with a 3-year follow-up to determine differences in progression. Of note, early presymptomatic repair (eg, at age 18) is the only real future solution, as no preventive method will fix the lesions. A 30% to 50% reduction of relevant saphenous disease may be the estimated benefit.

The second part of my study would relate to the discovery of long-term indicators of venous stasis in patients aged > 18 years and should include several hundred patients with CEAP C0–C1 disease. Stasis is the main factor of inflammatory degeneration of veins and, more specifically, valves. These sinus-located indicators, called *motion-resistant aggregates (MRA)*, consist of blood particles without a significant fibrin network (thus different from thrombus), and are well detected with newer ultrasound devices.[2] There are six consecutive MRA-marked stages, from alteration of sinus

hemodynamics to the onset of reflux (stages R1–R4, potentially reversible), followed by regression and loss of valve structures (stages R5–R6, not reversible).[2] The letter "R" indicates the intention to evaluate reversibility of low-flow damage by known "preventive" measures (eg, physical training, compression stockings, medication) in study subgroups with 3, 6, and 12 months of follow-up. This mode of valve damage is the only one justifying expenses for prevention! The benefit would be cost-effective prevention of stasis-related, acquired valve damage in presymptomatic stages.[3]

Additionally, there is the mechanism of pressure-induced valve decompensation. This is the way primary perforator leakage or terminal great saphenous vein valve reflux originates. It does not necessitate having a strenuous job or being an athlete—many activities may overstress a valve location of minor resistance. Repair or ablation of this location is an easy solution. This mechanism is the most benign of the three discussed (and easy to reverse by novel internal compression). Documentation of these lesions in the patients examined for the first and second parts of my suggested study should be sufficient.

The final part of my suggested ultrasound study is a computer-based exploration of the collected valve patterns thus far in order to differentiate the effects of superimposition. Congenital valve lesions, pressure-induced valve damage, and long-term acquired valve degeneration will maintain some primary features, but hemodynamic interactions may mask origins and sequelae. If we are able to read the individual history of vein disease, we will be able to reduce the expense of prevention by focusing on cases with a real benefit as well as reduce treatment costs by effective focal repair in the early stages of insufficiency. All this is simply copying the successful strategy of dentistry for caries. Both diseases are permanently threatening, but they're only chronic if we don't care. ■

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