Chapter 5

Mapping the future: Organizational, clinical, and research priorities in venous disease

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INTRODUCTION

Perhaps more so than in other areas of medicine and surgery, the management of acute and chronic venous disease remain somewhat diffuse. A wide variety of medical and surgical specialties are responsible for the prevention, diagnosis, and treatment of acute deep venous thrombosis (DVT), and patients with chronic venous disease (CVD) may be managed by primary care physicians, dermatologists, interventional radiologists, phlebologists, general surgeons, vascular medicine specialists, and vascular surgeons. Each may have a different approach to venous disease depending on their practice demographics, experience, and training. Furthermore, although the standard of care for acute venous thromboembolism has been established by randomized clinical trials and evidence-based guidelines have been developed,[1] outcomes such as the post-thrombotic syndrome have received inadequate attention, potential adjuncts such as thrombolytic therapy have not been adequately evaluated, and there remain problems with widespread dissemination of the guidelines. In the case of chronic venous disease, many treatment approaches are based on observational data and have not been subjected to rigorous trials. Furthermore, the current approaches to some problems, such as post-thrombotic deep venous incompetence and the prevention of ulcer recurrence, remain inadequate.

Under the auspices of the American Venous Forum (AVF), the 5th Pacific Vascular Symposium was envisioned as a process to address many of the problems existing in our understanding and management of acute and chronic venous disease. The goals of the meeting were to define the current state of knowledge in acute and chronic venous disease, and using this information as a baseline, to identify areas of deficiency, establish priorities, and map the future of venous disease with respect to needed research, professional and patient education, organization of the field, and management of acute and chronic venous disease. This was accomplished through a process of professionally facilitated appreciative inquiry[2] involving collaboration among experts from epidemiology and clinical trials, dermatology, hematology, interventional radiology, phlebology, and vascular medicine and surgery as well as representatives from industry and the National Institutes of Health. The assembled experts were organized into four groups addressing acute venous disease, the hemodynamic and diagnostic evaluation of venous disease, primary chronic venous disease, and secondary chronic venous disease. A final breakout group, the International Compression Club, evaluated the current status and future needs of medical compression hosiery.

The current state of knowledge in each of these areas has been reviewed in the previous sections of this supplement and provided the basis for developing future priorities for the field. Several of the priorities crossed group designations and are discussed first below. These are followed by the individuals groups' recommendations for advancing the future of venous disease, both in terms of overall priorities and specific initiatives that can be begun immediately.

ADVANCING THE ART AND SCIENCE OF VENOUS DISEASE

Organizational initiatives

The American Venous Forum (AVF), with a few exceptions, is largely composed of vascular surgeons. However, physicians from several specialties participate in the care of patients with acute and chronic venous disease and more cooperative efforts across key specialties are needed. Such efforts need to include vascular surgeons, dermatologists, hematologists, interventional radiologists, cardiologists, and field specific scientific experts in areas such as basic science, epidemiology, and genetics. Unless the quality of scientific collaboration and functional infrastructure are comprehensively improved and promoted (designated "we" priorities), priorities referring to the delivery of medicine from the physician to the patient ("me" priorities) are unlikely to advance effectively. Consistent with these goals,

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Competition of interest: none

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there was consensus that the American Venous Forum should direct efforts towards becoming a more broadly inclusive organization. As part of its scientific mission, the forum should move to establish a clearinghouse for projects related to venous disease, allowing experts to collaborate on specific initiatives. Such measures could include development of a nonprofit foundation to consolidate funding from disparate sources. The focus should be on highest quality evidence and credibility; this could be best achieved by collaboration between healthcare organizations, government funding agencies, industry, and members of the AVF and associated groups. A more unified, broadly inclusive organization would build a culture of cooperation and common purpose among venous specialists.

With the purpose of strengthening, consolidating, and coordinating the resources of existing organizations; raising awareness about venous disorders among physicians and the public; and fostering relationships among those with an interest in all aspects of venous disease; formation of a Joint Venous Council was recommended. Council members would include representatives from the major societies, industry, government, and the public. This group might be structured similar to the peripheral arterial disease (PAD) coalition that has focused on issues relating to peripheral arterial disease. A steering committee has been formed to implement this proposal and will develop an organizational framework, propose membership of the Joint Council, and plan an agenda for the first meeting.

A second universal theme was the need to develop a new training paradigm to properly train physicians in the diagnosis, treatment, and investigation of the entire spectrum of venous disorders. There is a clear need for an organized, evidence-based postgraduate venous curriculum. The development of an "angiology" specialty was suggested as a long-term goal to be discussed at future meetings. Creation of dedicated venous clinics with accreditation standards and a focus on education would be part of this project. Significant resources should also be devoted to educating nonspecialists (especially in the primary care and hospital settings) in the prevention of deep venous thrombosis and leg ulcers.

A global information system to facilitate reporting of venous disease was also considered important in advancing communication among investigators. Such a system could be used to develop and implement longitudinal epidemiologic studies characterizing the demographic, environmental, anthropomorphic, and social factors that lead to development of chronic venous disease in an international population. It would be useful in standardizing clinical trials of venous thrombosis, as well as evaluating drugs and devices for the treatment of venous disorders. Such a system could also improve the education of practicing physicians, private and governmental health care agencies, and the public.

Finally, all groups agreed to the need for increased governmental recognition of the importance of venous disease and innovative approaches to research funding incorporating both private commercial investment and governmental funding.

Clinical and research initiatives

The therapy of venous disorders must become more organized and evidence-based and should include development of better drugs for acute and chronic venous disease, as well as refinement of existing surgical procedures and development of new procedures and devices. Potential new devices for the treatment of venous disease include improved stenting systems, biodegradable filters, venous conduits, angiogenesis factors, artificial valves, and skin replacements. A better understanding of the interaction among devices and the coagulation and inflammatory systems will be required to properly assess any new device. Quality of life assessments must also be part of the evaluation of any new drug, device, or therapeutic approach to venous disorders, and the associated psychosocial problems need to be more fully addressed. Finally, from a clinical perspective, the development of integrated, multidisciplinary teams is essential in the treatment of patients with more advanced manifestations of CVD.

ACUTE VENOUS THROMBOEMBOLISM

The acute venous disease study section was charged with developing global programs to promote the awareness and prophylaxis of venous thromboembolic disease (VTE) as well as developing specific scientific projects to improve present standards of care. Several sessions were devoted to the identification of projects that would advance the treatment of venous disease through emerging technologies in clinical and basic science. From these discussions came three specific research endeavors that could be implemented in the next funding cycle. Many other potential initiatives were discussed, with the goal of using this meeting to launch future projects.

General priorities in acute venous thromboembolism

Several areas of need were identified and discussed in enough detail to initiate corrective measures and scientific studies in the near future. The need for a cooperative, interdisciplinary approach to venous disease; the advantages of a multidisciplinary, multicenter approach to research; and the need for a partnership between governmental funding agencies and industry has been discussed above. From an organizational standpoint a network of physicians interested in clinical protocols and basic research is also needed. This network should be internet-based and must be responsive to government-sponsored requests for proposals and industrial opportunities. Increased involvement of the AVF research committee in coordinating a web article repository, serving as a clearinghouse for Pacific Vascular V reports, and organizing lifeline venous research presentations is also needed.

From a research perspective, the basic mechanisms of venous thrombosis initiation and resolution need to be further investigated with the goal of designing future clinical trials in a hypothesis driven manner. Crucial to further

efforts is the integration of acute DVT outcomes research with therapies to improve and standardize patient care.

Specific research initiatives in acute venous thromboembolism

Three specific research projects were identified as warranting immediate attention and planning.

Strategies for early thrombus removal. Despite encouraging results from large multicenter registries[3] and small trials,[4,5] there is a lack of randomized clinical trial data supporting the use of early thrombus removal techniques in the treatment of acute DVT and such strategies are not routinely recommended by current consensus guidelines.[1] There is a clear need for generalizeable, randomized clinical trials comparing standard anticoagulation with "open vein" strategies designed to remove thrombus early after presentation with mechanical or pharmacological catheter-based thrombolytic techniques. Such trials should be of an international, multicenter design with anatomic stratification (iliofemoral vs femoropopliteal thrombosis) of patients. The design should include a 1-year run-in period to bring all centers online and perform early harm analysis. There was consensus in allowing some latitude with respect to the specific technique of thrombus removal (mechanical, pharmacological, or combination) to accommodate improvements in technology. Emphasis was placed on 5-year as well as 1-year outcomes with respect to quality of life, rate of recurrent VTE, and objective development of the post-thrombotic syndrome.

It is notable that a similar initiative, comparing best medical therapy vs best interventional strategy for thrombus removal, was recently designated the highest research priority at a multidisciplinary consensus panel arranged under the auspices of the Cooperative Alliance for Interventional Radiology Research (CAIRR) and the Society for Interventional Radiology (SIR).[6] The trial proposed by this panel is currently in the initial development and funding stages. The participants at the Pacific Vascular Symposium broadly supported such a trial and agreed to assist in the design and implementation of a definitive study as needed.

Defining the role of inferior vena cava (IVC) filters. The safety of permanent filters, as well as the development of retrievable filters, has led to their expanded use for a number of perceived relative indications[7,8] without substantial evidence to support such practices. Trials comparing the use of permanent and retrievable IVC filters with prophylaxis and DVT surveillance strategies in high-risk patients (eg, trauma and intracerebral hemorrhage) are desperately needed. The development and implementation of such a trial would optimally involve the participation of trauma surgeons and intensive care specialists. Trial endpoints should include survival, incidence of VTE, cost, length of ICU and hospital stay, and device specific complications such as IVC patency and filter migration.

Biomarkers in defining prognosis and determining duration of anticoagulation after acute DVT. Preliminary data suggests that the levels of fibrinolytic inhibition and activated coagulation are related to the extent of recanalization.[9] Furthermore, although the duration of anticoagulation is currently based on the risk of recurrent VTE, determined by randomized clinical trials,[1] observational data suggests that incomplete recanalization documented by ultrasonography[10,11] and persistently elevated D-Dimer levels[12] after discontinuing oral anticoagulants are important risk factors for recurrence. There is a need for robust management trials of specific markers of coagulation (D-Dimer, thrombin-antithrombin complex, microparticles, prothrombin fragment 1 + 2) and fibrinolysis (t-plasminogen activator and plasminogen activator inhibitor-1) in determining the type and duration of therapy for acute VTE. Endpoints would include thrombus extension, recanalization, and recurrent VTE. Biomarkers would be quantified at presentation, 1 week prior to discontinuation of therapy and 4 weeks following the completion of therapy. Patients would be followed for at least 2 years to document endpoints.

Other research priorities in acute DVT. Other studies proposed, but not developed in detail, included development of a test or panel of tests (a "thrombochip") to stratify the risk of VTE and predict outcomes after acute DVT. Such knowledge would permit interventions and duration of therapy to be individualized based on genomic, proteomic and serum biomarker profiles. Studies defining the true natural history and appropriate management of both secondary upper extremity DVT and proximal saphenous thrombophlebitis are also needed. There is clearly no consensus regarding the treatment of superficial thrombophlebitis and a registry may be more appropriate than a formal trial as an initial step. Projects including strategies to promote DVT awareness and improve compliance with established American College of Chest Physician (ACCP) guidelines[13] were also encouraged. Multicenter projects to generate support for young investigators and to assist with AVF sponsored submissions to the NIH were also proposed.

VENOUS DIAGNOSTICS AND HEMODYNAMICS

This group focused on unresolved issues and future projects involving the diagnosis of acute and chronic venous disease. As venous diagnostic testing requires a thorough understanding of venous physiology and hemodynamics, this group was termed the diagnostics/hemodynamics group. After preliminary discussions in breakout groups, the diagnostics/hemodynamics group developed plans and recommendations for research projects relevant to venous diagnosis.

General priorities in venous diagnostics and hemodynamics

The initial discussions of the diagnostics/hemodynamics group were broadly focused and several ideas were advanced. Future research should focus on the identification of molecular, serologic, and genetic markers that may be useful in detecting venous disease apriori, perhaps in conjunction with targeted thrombophilia testing and as-

sessment of environmental risk factors. Such information might facilitate more individualized treatment of patients with acute venous thrombosis and chronic venous disease and aid in identifying the contribution of individual risk factors to the overall risk of venous thrombosis.

Further work is needed to improve our understanding of venous physiology, pathophysiology, and natural history. This is fundamental to improving diagnostic tests and facilitating precise treatment of patients with venous disorders. The development of a quantitative test for venous obstruction and a global noninvasive surrogate measure of ambulatory venous pressure are particular priorities. In addition, there is a critical need to standardize existing venous tests with respect to indications, testing protocols, and normal ranges. A clear definition of what constitutes a significant change in a testing parameter is particularly needed in patients with advanced CVD who may undergo interventions.

Specific research initiatives in venous diagnostics and hemodynamics

Based on these preliminary deliberations, the following projects have been identified as priorities in advancing our understanding of venous hemodynamics and improving diagnostic modalities.

Investigating venous disease evaluation and standardization of testing (INVEST). The goals of this project are to standardize noninvasive testing for acute and chronic venous disease; identify standard quality of life and hemodynamic outcomes; and develop uniform testing protocols. As initially proposed, this project involves three phases. First, the diagnostic modalities currently being utilized in vascular laboratories must be determined. Potential sources of data include the Intersocietal Commission for Accreditation of Vascular Laboratories (ICVAL) database, which can be used to identify tests actually being performed as well as the indications, protocols, and exam and interpretation standards of various vascular laboratories. The Center for Medicare and Medicaid Services (CMS) can also be queried for ICD-9 and CPT codes to define the range of tests performed, the indications for testing, and the demographics of those ordering examinations. Members of the venous societies can also be surveyed for their testing practices in patients with acute and chronic venous disease. Secondly, a comprehensive literature review should be undertaken to examine the tests and standards used in current venous research. Finally, appropriate societal representatives should evaluate the above data and a consensus statement developed regarding protocols for noninvasive venous testing, normal ranges, the definition of significant within patient change, and recommended examinations based upon common clinical presentations. These suggestions would be added to the existing reporting standards for venous disease.[14-16]

MR outflow obstruction of venous disease (MOOVD). Magnetic resonance venography (MRV) is among the most promising modalities in venous diagnostic testing. This project aims to explore the use of MRV in assessing venous obstruction. Potential methods of interest include CINE-gated MRV to quantify outflow obstruction. Soft tissue water content should also be evaluated as a potential diagnostic measure. Pre- and post-therapy testing will be performed along with blood tagging (eg, with gadolinium) studies to evaluate venous inflow and outflow.

Assessment of reflux and symptomatic evaluation (ARSE). This study proposes to evaluate the anatomic patterns of reflux and hemodynamic parameters that most accurately identify individual CEAP categories, forecast disease progression to higher CEAP classes, and predict response to therapy (quality of life, ulcer healing). Reflux will be evaluated from the inguinal ligament to the ankle using duplex ultrasonography and standing cuff deflation methods.[17] Diagnostic measurements will include duration of reflux, reflux velocity, reflux volume, reflux velocity index, and perhaps other as yet unknown parameters. An Incompetent Valvular Severity Score will be developed to quantify the overall severity of reflux. A multicenter design is required to provide adequate patient numbers and insure inclusion of patients with varying demographics. Subjects with lymphedema, recent trauma, BMI > 40, and previous vein surgery would be excluded.

Duplex ultrasound in a multicenter study of acute DVT (DUMSAD). Most validated strategies for the diagnosis of acute DVT have limited examination to compression of the proximal veins and have required either serial examinations[18,19] or combined algorithms including D-dimer measurement and clinical risk stratification.[20-23] Despite encouraging preliminary data,[24,25] the accuracy of a single, technically adequate duplex scan, including the calf veins, has not yet been sufficiently validated.

The purposes of this study are to evaluate the accuracy of a single color flow duplex examination, including the calf veins, in excluding acute DVT; to improve guidelines for the diagnosis of acute DVT; and to define an adequate scan technique. Subjects should have no prior history of DVT and be clinically symptomatic. In addition to clinical and demographic information, collected data will include physical examination (including calf circumference), clinical probability scores, and D-dimer and CRP levels. Complete, bilateral color flow duplex scans will be performed including measurement of thrombus location, length, volume, and echogenicity as well as venous diameter and wall thickness. Subjects with negative scans but a high clinical probability of DVT will undergo serial imaging. As comparison with venography would be difficult, this will be a management trial with endpoints including the results of clinical and ultrasound follow-up at 6 months.

Outcome relation to thrombus characteristics (OTC). The purposes of this study are to evaluate the natural history of DVT, including the development of reflux, in relation to ultrasound characteristics of the thrombus. Thrombus specific measurements will include the extent and location of the thrombus, degree and length of time to recanalization, grey-scale characteristics of the thrombus, and the development of reflux and its timing. Analysis will include the effects of type of anticoagulation

(low molecular heparin vs unfractionated heparin), the use of other adjuvant therapies, and serum markers of coagulation, fibrinolysis, and inflammation.

PRIMARY CHRONIC VENOUS DISEASE

The working framework for the primary chronic venous disease group was subdivided into topics including prevention, pathophysiology, diagnostics, research, and treatment and intervention.

General priorities in primary chronic venous disease

The combination of declining health care budgets and an increasing number of patients with CVD will soon render the issue of funding care for complications of primary CVD critical. Population screening for early disease will likely become indispensable in containing the socioeconomic repercussions of primary CVD by enabling timely intervention and prevention of disease progression. Control of associated risk factors; genetic interventions in CVD-related aberrations; selective, safe and long-lasting suppression of inflammatory processes; and national awareness of primary CVD are also essential in disease prevention.

Optimal treatment of CVD is currently hindered by insufficient knowledge of the pathophysiology, including the sentinel events preceding CVD progression and the effects of inflammation, re-epithelialization, matrix deposition, and tissue remodeling. An improved understanding of these pathophysiologic mechanisms, through clinical and basic research, is critical to further advancements in disease prevention and management.

Comprehensive, cost-effective, and minimally invasive diagnostics must be developed to facilitate both early identification of CVD and quantification of the associated pathophysiology. Three-dimensional, limb specific imaging equipment providing accurate data on the anatomy, hemodynamics, and cytochemical interactions can be envisioned in the near future. Such progress would certainly promote the development of new therapies optimized for clinical efficacy, invasiveness, adverse effects and cost-effectiveness. Treatment assisted by robotics, innovative drugs, gene therapy, high-technology compression hosiery, and endovalves would greatly improve currently available surgical techniques.

Development of such therapies will require a thorough reorganization of existing practices and institutions. There is a clear need for evidence-based management protocols in CVD. Geographic centers of clinical excellence, collectively cooperative, and a Central Venous Disease Clearing House (eg, National Institute for Venous Clinical Excellence) might facilitate clinical and academic progress while safeguarding professional cohesiveness and ethical integrity.

Based upon these considerations, the following priorities (in declining order) were proposed by the primary chronic venous disease group.

(a) The development of minimally- or noninvasive techniques for restoring vein function;
(b) Enhancement of public and physician awareness of primary CVD;
(c) Identification of important, quantifiable determinants of outcome at the macro-/micro-circulation and tissue levels;
(d) Identification of tissue markers and precursors of primary chronic venous disease development;
(e) Identification of genetic and environmental factors leading to primary venous disease;
(f) The development of pharmaco- and physical-therapies for primary chronic venous disease prevention and treatment.

Specific research initiatives in primary chronic venous disease

Core lab consortium and genetic database. A core laboratory consortium to collect samples of blood, vein, skin, and other pertinent tissues would foster working relationships among investigators and expedite both clinical and basic science research. Samples and de-identified demographic data would be stored by the consortium and made available to participating institutions. Academic investigators, the pharmaceutical industry, and other institutions undertaking venous research or research linked to venous specimens (internal medicine, rheumatology cardiology, etc.) would have access to the tissue bank. Potential targets for investigation would include proteonomics, evaluation of up-regulated or down-regulated genes, and inflammatory markers as well as their correlation with pathophysiological and clinical data. An initial goal of collecting specimens from 200 subjects, with targeted investigation of several of these questions was proposed.

Endovenous valve repair. Despite the reported success of primary venous valve repair,[26-29] these procedures are not widely performed, at least partly because the procedures are perceived as complex with good results obtained only in a few centers having extensive experience. There is a clear need for a minimally- or noninvasive venoscopic valve repair to restore vein function. Making use of advanced stapling and suturing technology, this method would enable minimally invasive valve reconstruction, obviating the need for complex open surgery or vein ablation. The participation of industry would be required for design expertise, funding, prototype development, feasibility assessment, and animal testing.

Wireless, functional venous diagnostic tests (ISR-VDS). Many currently available diagnostic tests (Duplex ultrasonography, air plethysmography) require cumbersome diagnostic equipment that limits their application under truly physiological conditions. An innovative, screenless, real-time, venous duplex system, (ISR-VDS) would be a significant addition to the venous diagnostic armamentarium. Such a system would optimally use wireless, real-time, three dimensional, color duplex technology, delivered to the examiner through virtual reality eyewear and allowing superimposition of images on the surgical or endovascular field. Development of a system would likely require assistance from the military, computer and ultra-

sound industries for funding, development of a prototype, and initial animal and human testing.

SECONDARY CHRONIC VENOUS DISEASE

Occurrence of the post-thrombotic syndrome after an episode of acute DVT is related to both failure of recanalization, with persistent venous obstruction, and the development of valvular incompetence.[30,31] Important priorities in improving the care of patients with secondary chronic venous disease include prevention, development of diagnostic tests to precisely identify sites of abnormal venous function, and the development of technology to rectify chronic obstruction and secondary valvular incompetence.

General priorities in secondary chronic venous disease

Advances in the treatment of acute DVT are critical to the prevention of the post-thrombotic syndrome. Early, complete thrombus removal by mechanical, pharmacological, or surgical thrombectomy is likely an important adjunct in preventing chronic obstruction as well as vein wall and valvular damage. The need for multicenter, international randomized clinical trials comparing catheter-directed thrombolysis, endovenous mechanical thrombectomy, and surgical thrombectomy with standard anticoagulation alone has been detailed above. The development of oral thrombolytics and anti-inflammatory drugs that inhibit vein wall/valve fibrosis would be ideal. Finally, "thrombosis teams", with significant expertise in this field, should be organized at major healthcare centers.

It is known that previous deep venous thrombosis, heredity, and occupational prolonged standing contribute to the development of symptoms, but the pathophysiology and genetic determinants of CVD are largely unknown. Our current understanding of CVD suggests that is develops from the following sequence of events - initial pericapillary extravasation caused by inflammation is followed by formation of a fibrotic perivascular cuff with vascular proliferation, fibroblast recruitment, and fibrosis mediated by matrix metalloproteinases (MMPs) and other proteinases.[32-37] The capillary endothelium likely includes a mechanism that detects the hemodynamic changes produced by venous hypertension. Drugs such as pentoxyphilline and Daflon are believed to act by inhibiting leukocyte-endothelium interactions and reducing tissue edema.[38] However, advances in pharmacotherapy and other approaches, such as stem cell treatment, will be possible only through an improved understanding of the pathophysiological mechanisms underlying the progression from C0 to C6 disease. This must include a better definition of the genetic basis of chronic venous insufficiency (CVI), including inherited alterations in vein wall morphology, susceptibility to venous hypertension, and the influence of environmental factors. The phenotypes and genetic material of patients with CVD would optimally be correlated with CEAP classification and duplex ultrasound studies. The identification of genes associated with venous disease will need to be performed in collaboration with epidemiological studies in centers for genetic research.

The most useful diagnostic tools currently available are duplex ultrasonography, plethysmography, contrast venography, magnetic resonance venography (MRV) and computed tomography (CT). However, all have limitations and the severity of symptoms does not correlate with methods currently used to evaluate reflux and obstruction. The ideal imaging study should precisely localize and quantify reflux and obstruction within the deep, superficial, and perforator venous systems (global and segmental). Such a test should also be portable, cost effective, highly reproducible, and predictive of long-term outcome. A wireless device that can be applied at rest and enable real-time study during activity (equivalent to exercise ankle-brachial index (ABI) in arterial disease) as well as treatment simulation (eg, temporary superficial venous occlusion to predict outcome of saphenous ablation) would be optimal. Duplex ultrasonography and magnetic resonance imaging (MRI) are currently the most likely candidates for further development, but these may be replaced by other imaging modalities in the future.

The primary goal of surgical therapy is to improve venous insufficiency through the obliteration of major reflux pathways and relief from obstruction. Unfortunately, interventions aimed at restoring deep valve competence are less successful in secondary than in primary venous disease.[39] Furthermore, open interventions, such as venous bypass and valve repair, are performed only in highly specialized centers by experienced surgeons. However, minimally invasive techniques, potentially accessible to a broader group of specialists, have emerged in the past several years and their further development should be encouraged.

Specific research initiatives in secondary chronic venous disease

External compression devices. Compression stockings reduce edema, improve venous pump function, impede venous reflux, and may improve arterial inflow.[40-43] However, compliance is often poor due to too much or little compression, difficulty in applying the stockings, discomfort, and aesthetics. An improved understanding of the hemodynamic effects of compression would allow it to be targeted and optimized for the individual patient. This may also allow design of more comfortable, easier to apply stockings that achieve the desired hemodynamic effect.

Another approach to treatment of severe CVI associated with valve dysfunction would be an "external" valve closure compression pump that senses reflux and generates intermittent pressure peaks synchronized with the calf pump and specific for the degree of reflux and size of the leg. Such a device must be portable, easy to use, respond to patient movement and position, and give feedback to the physician.

Dedicated venous stents. Iliocaval obstruction can be treated by percutaneous insertion of stents.[44,45] However, current available stents are not specifically designed for the venous system and the development of in-stent restenosis requires frequent reintervention. Development of dedicated venous stents, including modular systems for the iliocaval confluence, is a priority in the treatment of secondary CVD. The characteristics of such a stent should include

higher radial strength, greater length and diameter, flexibility, low thrombogenicity, and minimal in-stent re-stenosis. The development of such a stent will require further investigation regarding stent-vein wall interactions, mechanisms of restenosis, and periprocedural pharmacotherapy.

Implantable venous valves. As discussed in the section on secondary CVD, there have been extensive efforts to develop a percutaneously implantable deep venous valve and there is preliminary data regarding the use of acellular valve xenografts in humans. However, late malfunction and thrombosis continue to be a problem with current designs. Further development of implantable venous valves is a critical priority and will require a prosthetic that is nonthrombogenic, nonimmunogenic, flexible, and adaptable to all venous segments. Development of artificial biosynthetic mechanical valves was also ranked as a high priority by the SIR multidisciplinary consensus panel.[46]

COMPRESSION HOSIERY

The mission of the International Compression Club (ICC) is to provide a forum in which medical experts interested in compression therapy and representatives from the manufacturers of compression devices can discuss controversial issues and propose solutions. Much of the discussion at the Pacific Vascular Symposium focused on the need to standardize compression parameters and reporting.

General priorities in compression hosiery

Compression is a medical treatment, requiring a precise knowledge of the dose (ie, pressure, stiffness) necessary to achieve the desired effect. Manufacturers currently provide a pressure range (mm Hg) based on in vitro measurements, as well as a designated compression class. Compression classes vary according to national regulations and are not comparable. The medical literature should abandon use of "compression classes", reporting the range of pressure in mm Hg and the method of measurement. Prescribing compression stockings on the basis of compression ranges, rather than classes, is also recommended.

There is a need to further evaluate current methods of pressure measurement, both in vivo and in vitro, with respect to the variability and reproducibility of different techniques. Compression stockings from all manufacturers should be independently evaluated using the three most common methods (Hatra, ITF, and Hosy).[47]

Stiffness, which is defined as the pressure change generated by an increase in the transverse stretch of the stocking, is not regularly declared by manufacturers. Use of the same method for designation of pressure and stiffness would be desirable in the future.

There is also a need to standardize the marketing of compression bandages. As a minimum requirement, complete information regarding the constituents (composition), stretchability (elasticity), adhesion (cohesive, adhesive, or nonadhesive), and dimensions should be provided on the packaging. With respect to elasticity, the following terminology is recommended:

Table I. Organizational initiatives of the Pacific Vascular Symposium

Initiative	*Goals*
Joint Venous Council	To form a new organization with the goals of • Increasing awareness about venous disorders among physicians and the public • Foster relationships with industry, government and national/ international societies
Redefinition of the American Venous Forum as a broad-based, inclusive organization	• The achieve influence through critical mass and clinical/ scientific excellence • To act as a project/grant clearinghouse • To create evidence-based practice guidelines

- No stretch 0% to 10% inelastic
- Short-stretch <100% inelastic
- Long stretch >100% elastic

Scientific reports utilizing compression bandaging should further define the application technique (eg, spiral, figure-of-8, Putter, etc), the degree of bandage overlap, the number of layers, the experience of the practitioner, and the pressure delivered. The pressure may be measured at various specified sites, but site B1 (gaiter area) is recommended as the standard for recording in vivo compression.[48] Pressure levels should be reported as follows:[49]

- Light 20 mm Hg
- Medium 20 to 40 mm Hg
- Strong 40 to 60 mm Hg
- Extra strong >60 mm Hg

Future innovations in compression bandaging should be directed towards medicated bandages; sprays applied after application to modify fixation, cohesion, and stiffness; new materials to improve comfort and compliance; pressure monitoring devices incorporated into bandaging; the combination of compression bandaging with intermittent pneumatic compression (IPC); and air- and water-filled devices.

The role of IPC in the treatment of deep venous thrombosis, edema, venous ulcers, combined arterial/venous ulcers, and causalgia also needs further definition. More definitive studies on the role of IPC in thromboprophylaxis are also needed. Future studies should focus on important clinical endpoints as well as the effect of IPC on markers of coagulation, fibrinolysis, inflammation, and angiogenesis.

IMUA–THE FUTURE OF VENOUS DISEASE

The goals of the Fifth Pacific Vascular Symposium were to establish the current state of knowledge in acute and chronic venous disease and develop a 10-year plan for

Table II. Research initiatives of the Pacific Vascular Symposium

Initiative	Goals
Evaluation of venous outflow obstruction	To explore the use of magnetic resonance venography in the evaluating and quantifying venous outflow obstruction
Duplex ultrasound in the diagnosis and prognosis after DVT	• To evaluate the utility of a single color-flow duplex exam, including the calf veins, in excluding DVT • To define standard scanning protocols • To produce guidelines for the diagnosis of DVT • To evaluate the natural history of DVT in relation to thrombus characteristics
Early thrombus removal (open vein strategies)	To evaluate the role of early thrombus removal in the management of acute DVT • Multicenter, international randomized clinical trial • Mechanical, pharmacological and surgical thrombectomy arms • Stratified for thrombus location (iliofemoral vs femoropopliteal) • Objective clinical and quality of life outcome measures
Biomarkers in diagnosis and prognosis of DVT	To evaluate the utility of coagulation, fibrinolytic, and inflammatory biomarkers in diagnosing DVT and providing prognostic information regarding type and duration of therapy
Core-lab consortium and genetic database	• Creation of a specimen bank (vein, skin, blood) with clinical data to facilitate CVD research • To identify markers predicting susceptibility and disease progression
Evaluation and standardization of venous testing	• To standardize acute and chronic venous disease testing • To develop uniform testing protocols • To define normal ranges and significant variations • To identify a standard for quality of life and hemodynamic outcomes
Assessment of reflux and its relation to CVD progression	• To identify patterns of reflux that correlate with CEAP categories • To identify patterns of reflux predicting progression to CEAP 4 to 6 • To identify patterns of reflux predicting success after intervention • To develop a severity score for valvular incompetence
IVC filters in high-risk patients	• To compare strategies of permanent filters, removable filters, and surveillance in patients with trauma and intracerebral hemorrhage
Endovenous valves and venoscopic valve repair	• To develop a nonthrombogenic, nonimmunogenic, flexible and adaptable prosthetic venous valve • To develop minimally invasive techniques to restore valve function
Pathophysiology of CVD	To assess the role of the endothelium and identify mechanisms of ambulatory venous hypertension, inflammatory skin changes, and ulceration in animal and clinical models
External compression devices	To develop a compression device to treat advanced CVD • Portable and easy to use • Responds to patient position and movement • Provides physician feedback
Dedicated venous stents	• To create a dedicated venous stent with greater radial strength and low thrombogenicity • To characterize the vein wall reaction to stents • To identify mechanisms of restenosis • To identify the role of periprocedural pharmacotherapy
Functional venous testing	• To develop wireless, functional venous tests enabling real time study during exercise

DVT, Deep venous thrombosis; *CVD,* chronic venous disease.

advancement of the field. As detailed in the previous sections of the meeting proceedings, the first part of this goal, establishing the current state of knowledge, was successfully accomplished. Additionally, several organizational and investigative priorities were established, initial protocols developed, and experts recruited to participate in the individual projects. Perhaps most importantly, definitive plans were made to guide overall progress and identify priorities for AVF support through establishment of an IMUA (Hawaiian for moving forward in a positive direction) committee.

The committee has distilled the initiatives generated by the four working groups into two organizational (Table I) and 13 investigative projects (Table II), each with an appointed volunteer coordinator. Some validation of the importance of the research initiatives is provided by the observation that many similar projects were ranked as a high priority by an independent multidisciplinary consensus panel organized by the SIR.[6,46] As discussed above, the ability to accomplish these projects will require innovative approaches to funding including partnerships with The National Institutes of Health (NIH) and other governmental agencies, industry, the American Venous Forum, and other interested societies. Initial investigator's meetings are currently underway, and it is anticipated that draft protocols and funding proposals will be developed within the next year. Further information, includ-

ing contact information for interested investigators, is available on the American Venous Forum website (http://www.venous-info.com/).

Despite the progress made during the Fifth Pacific Vascular Symposium and the importance of these individual initiatives, the broader goal of defining a 10-year plan for the advancement of venous disease was only partially accomplished and should continue to be addressed in future meetings.

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