Research Priority Documents Leading the Way in Venous Diseases

Interdisciplinary task forces are key to identifying unmet needs in basic science, translational, and clinical trials research for venous disease and improving practice.

By José Antonio Diaz, MD

Although knowledge in medicine advances rapidly, gaps in disease mechanisms remain to be uncovered. Deep vein thrombosis (DVT) is an example. An example of research efforts advancing our understanding of this disease process is the discovery of the coagulation cascade, which allowed researchers to develop new oral anticoagulants.

Additionally, recent discoveries, such as the role of neutrophil extracellular traps[1] and galectin-3,[2] open the options for new biomarkers and potential therapeutic targets in venous thrombosis. This reflects the great basic science efforts, but also that there is a mystery to be solved, biologically speaking. Both discoveries were performed in basic science laboratories and translated to patients, with potential roles that need to be further explored.[3,4]

Finding gaps in knowledge and unmet needs is the scientist's motivation to investigate. In 2009, Glynn et al published a revolutionary study indicating that statins may prevent venous thromboembolism (VTE).[5] The authors concluded that they found a significant reduction in the risk of developing VTE in the studied patient population. Part of the discussion reads, "Overall, validation of our results and further elucidation of the potential mechanisms will be important to confirm our findings," and in 2013, one of the first mechanistic manuscripts was published.[6] This investigation was a basic science, preclinical trial on discovering the mechanisms behind the non–lipid-lowering effect of statins after the JUPITER trial. Defining the application of statin on venous thrombosis patients remains to be determined, but we now understand why statins may prevent VTE. This example demonstrates the importance of basic science and preclinical trials to support clinical research.

Recent publications have demonstrated the importance of interdisciplinary groups collaborating to identify gaps and highlight research priorities. Experts enumerated and justified research questions that need to be answered by the research community to improve current practice. This article summarizes research priorities that have been identified in submassive pulmonary embolism (PE), pelvic venous disorders (PeVDs) in women, and VTE.

RESEARCH PRIORITIES FOR SUBMASSIVE PE

As part of a 19-member multidisciplinary research consensus panel, Sista et al published research priorities for submassive PE, addressing the questions of where are we and where we need to be on short- and long-term outcomes.[7] The meeting had three sessions: current knowledge, trial design and methodology, and research network infrastructure. In the current knowledge session, they discussed systemic thrombolysis for acute submassive PE, catheter-directed thrombolysis (CDT) for acute submassive PE, catheter-based thrombus extraction devices, long-term outcomes after PE, and clinical trials evaluating treatments of pulmonary hypertension and chronic thromboembolic pulmonary

hypertension. In the trial design and methodology session, they discussed challenges in conducting an interventional versus medical trial, how many treatments should be evaluated, and trial outcomes. In the research network infrastructure, they discussed the recent creation of the National PE Response Team Consortium and patient engagement in clinical research. At the end of each session, there was an open forum that addressed predefined questions and panel-initiated questions. The group concluded that a randomized trial of CDT plus anticoagulation versus anticoagulation alone is the primary research priority. The primary efficacy endpoint should assess and capture long-term health, and the primary safety endpoint should be bleeding and other periprocedural complications.

This was a great interdisciplinary panel for setting up research priorities in this venous disease area. The nature of the group was clinically oriented, but basic science or preclinical studies were not discussed during the process or included in the research priorities.

RESEARCH PRIORITIES FOR PeVDs IN WOMEN

Khilnani et al published recommendations for PeVDs in women from another multidisciplinary research consensus panel.[8] The interdisciplinary group included 11 members, and representatives solicited from medical societies with a shared interest in chronic venous pain and pelvic-derived lower extremity varicose veins in women. The specialties were represented by three gynecologists, four interventional radiologists, two vascular surgeons, a health outcomes scientist, and a former medical director of a large health care insurer panel. All panelists had significant academic or clinical experience in PeVDs, and an audience including patients, other providers, and representatives from insurance carriers, the National Institutes of Health, FDA, and industry were also invited to participate.

The format included a 1-day panel meeting divided into sessions.[8] The first session included expert presentations to review the available evidence and identify gaps. This was followed by a second session involving discussions to define further the critical research questions that need to be addressed. Panel presentations included chronic pelvic pain (CPP) in women (prevalence, impact, evaluation, differential diagnosis, and introduction to management), pathophysiology of PeVDs, patient-reported outcome instruments for women with CPP, imaging of PeVDs, outcomes of embolization in women with CPP, surgical and endovascular options and outcomes for treatment for clinically significant iliac and renal vein compression, treatment options for pelvic-origin lower extremity and vulvar varicose veins, and gynecologic options and outcomes for PeVDs.

The most critical research priorities identified by the panel were a consensus on the clinical and imaging criteria for PeVD, a discriminative tool to categorize patients with PeVD, and quality-of-life tools to measure the health burden in women affected by PeVD and its change after treatment.[8] The panel also recommended international interdisciplinary involvement in the research plan to gain a broad endorsement of the disease definitions and tools.

Although randomized controlled trial data are needed, the panel was clear that it is necessary to first develop the required research tools to ensure that the financial and time investments made to support PeVD research will yield evidence that will be broadly accepted.[8] In agreement with the authors, I would like to emphasize this last critical and realistic statement.

RESEARCH PRIORITIES FOR VTE

Finally, in a scientific statement from the American Heart Association (AHA) and the International Society on Thrombosis and Haemostasis (ISTH), Cushman et al presented a VTE research priorities document in a translational research manner, which was divided into five research levels: fundamental (T0), human (T1), patient (T2), practice (T3), and population (T4).[9,10] The project included members of 16 international organizations, including lead organizations for this project (AHA, American Venous Forum, and ISTH), who were invited to a crowdsourcing activity to share their priorities for VTE research through a survey.

This manuscript included the spectrum of translational research (bench-to-bedside-to-population), and the summary of the identified research priorities for each level were as follows[9,10]:

- T0: Identify the mechanisms responsible for the approximately 50% of patients with unprovoked VTE and better understand the mechanisms that differentiate hemostasis from thrombosis
- T1: Develop new methods for diagnosing, treating, and preventing VTE
- T2: Identify biomarkers to improve diagnostic, follow-up, and treatment. New treatments, such as catheter-based therapies, require further testing to identify which patients are most likely to benefit
- T3: Identify evidence-based tools to improve care delivery
- T4: Promote public awareness campaigns and develop large, population-based cohort studies to understand the biologic and environmental conditions that favor the development of VTE and its complications

The authors encouraged the funding of agencies and training programs to support scientists and clinicians who work in interdisciplinary teams to solve VTE.[9,10] This work presented research priorities from the bench to the community and highlighted the importance of including all research areas—a model that should be followed by future research priorities endeavors when possible.

CONCLUSION

The lack of full understanding of disease processes and the rapid advances in technology from research and development efforts favor the development of interdisciplinary task forces to identify unmet needs in both areas. In addition, identifying research priorities as a result of interdisciplinary action help guide future research efforts, which ideally should include all research areas, from the bench to the patient. ■

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José Antonio Diaz, MD
Research Associate Professor of Surgery
Director of the Division of Surgical Research
Light Surgical Research and Training Laboratory
Vanderbilt University Medical Center
Nashville, Tennessee
jose.a.diaz@vumc.org
Disclosures: None.