

AHA/ISTH SCIENTIFIC STATEMENT

Venous Thromboembolism Research Priorities

A Scientific Statement From the American Heart Association and the International Society on Thrombosis and Haemostasis

Endorsed by the American Venous Forum

ABSTRACT: Venous thromboembolism is a major cause of morbidity and mortality. The impact of the US Surgeon General's *The Surgeon General's Call to Action to Prevent Deep Vein Thrombosis and Pulmonary Embolism* in 2008 has been lower than expected given the public health impact of this disease. This scientific statement highlights future research priorities in venous thromboembolism, developed by experts and a crowdsourcing survey across 16 scientific organizations. At the fundamental research level (T0), researchers need to identify pathobiological causative mechanisms for the 50% of patients with unprovoked venous thromboembolism and to better understand mechanisms that differentiate hemostasis from thrombosis. At the human level (T1), new methods for diagnosing, treating, and preventing venous thromboembolism will allow tailoring of diagnostic and therapeutic approaches to individuals. At the patient level (T2), research efforts are required to understand how foundational evidence impacts care of patients (eg, biomarkers). New treatments, such as catheter-based therapies, require further testing to identify which patients are most likely to experience benefit. At the practice level (T3), translating evidence into practice remains challenging. Areas of overuse and underuse will require evidence-based tools to improve care delivery. At the community and population level (T4), public awareness campaigns need thorough impact assessment. Large population-based cohort studies can elucidate the biological and environmental underpinnings of venous thromboembolism and its complications. To achieve these goals, funding agencies and training programs must support a new generation of scientists and clinicians who work in multidisciplinary teams to solve the pressing public health problem of venous thromboembolism.

Mary Cushman, MD, MSc, FAHA, Chair
Geoffrey D. Barnes, MD, MSc, FAHA, Vice Chair
Mark A. Creager, MD, FAHA
Jose A. Diaz, MD, FAHA
Peter K. Henke, MD, FAHA
Kellie R. Machlus, PhD
Marvin T. Nieman, PhD, FAHA
Alisa S. Wolberg, PhD, FAHA
On behalf of the American Heart Association Council on Peripheral Vascular Disease; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Epidemiology and Prevention; and the International Society on Thrombosis and Haemostasis

Key Words: AHA Scientific Statements
■ hemostasis ■ postthrombotic syndrome ■ pulmonary embolism
■ research priorities ■ thrombosis
■ venous thromboembolism ■ venous thrombosis

© 2020 by the American Heart Association, Inc., and the International Society on Thrombosis and Haemostasis.

<https://www.ahajournals.org/journal/circ>

Venous thromboembolism (VTE) remains a major cause of morbidity and mortality, affecting up to 1 million Americans and >700 000 Europeans annually.¹ Composed of both deep vein thrombosis (DVT) and pulmonary embolism (PE), VTE disproportionately impacts older adults worldwide.² An estimated 1 in 12 people will develop VTE after 45 years of age.³ Thirty-day mortality is as high as 30% for patients with PE.⁴ Emerging knowledge suggests impaired quality of life is common. Up to 50% of DVT patients will develop postthrombotic syndrome (PTS), which consists of pain, swelling, skin changes, and ulceration; 5% to 10% will have severe morbidity with reduced quality of life.⁵

In 2008, the US Surgeon General issued *The Surgeon General's Call to Action to Prevent Deep Vein Thrombosis and Pulmonary Embolism*.⁶ That document highlighted the unique opportunity for multiple stakeholders to coordinate efforts aimed at (1) increasing public awareness, (2) supporting development of evidence-based practices, and (3) carrying out research to address gaps in knowledge. It is unclear how much progress has been made in the decade since that call to action. Although some organizations champion patient, provider, and public awareness, efforts in translational and transformative research are not commensurate with the public health impact of VTE.⁷

This statement outlines key research priorities to address knowledge gaps in VTE (Table). As outlined in the [Data Supplement](#), in 2018, members of 16 international organizations, including lead organizations for this project (the American Heart Association, the American Venous Forum, and the International Society on Thrombosis and Haemostasis), were invited in a crowdsourcing activity to share their priorities for VTE research through a survey. Although attempts were made to include a global perspective, we did not collect participant location, and North American participation may be overrepresented. Informed by these results, invited experts presented their vision at the 2018 American Heart Association Vascular Discovery conference (San Francisco, CA), and the audience provided input. At that meeting, a writing group was formed to develop this scientific statement based on survey results. The final statement outlines key areas for future research across the spectrum of translational research (bench-to-bedside-to-population; Figure). As this article was going to production, the rapid realization of a new coagulopathy with marked VTE risk related to coronavirus disease 2019 (COVID-19) has led to a pressing need for basic, translational, and clinical research, including on antithrombotic treatments in these patients.

Table. Some Research Priorities in VTE Across the Spectrum of Translational Research

T0—Fundamental and discovery-based research	
Uncover mechanistic differences between hemostasis and thrombosis	
Specify individual and interacting roles for cellular, biochemical, and biophysical (flow) functions and thrombogenesis	
Explore effects of vascular wall dysfunction and blood flow on thrombus formation	
Develop robust animal models of PE that mimic human disease	
Understand limitations and appropriate use of specific VTE preclinical models	
Distinguish mechanisms of in situ thrombosis vs embolization	
T1—Human level research	
Develop imaging tools for diagnosis that characterize thrombus chronicity and embolic potential	
Identify new targets for anticoagulant therapies	
Combine imaging findings with biomarkers (circulating factors, genomics, etc) to identify populations most likely to benefit from VTE prophylaxis or treatment	
Identify the role of novel biomarkers to predict VTE recurrence risk	
Explore the efficacy of VTE treatment strategies based on thrombus characteristics instead of duration	
T2—Patient level research	
Identify patients most likely to benefit from catheter-based therapies in both PE and proximal DVT	
Explore the role of adjuvant therapies (eg, statins, P2Y12 inhibitors) to prevent postthrombotic syndrome	
Identify causes of breakthrough VTE despite adequate prophylaxis	
Improve prediction and understand clinical course of VTE in pediatric populations	
Define thresholds for VTE prophylaxis and appropriate dosing in those at risk of VTE, including pregnant patients	
T3—Practice level research	
Study methods to better implement VTE trial evidence into clinical practice, including both overuse and underuse of VTE-specific therapies	
Explore the role of the electronic medical record and population health tools intended to drive appropriate clinical care	
Study effectiveness of devices for PE and DVT treatment (vena cava filters, thrombus retrievers, etc) using population-based registries	
Define the safety and efficacy of DOAC therapy in special populations	
Define the clinical and nonclinical impacts of thrombophilia testing in patients, their families, and the population at large	
T4—Community and population level research	
Assess the impact of public awareness campaigns about VTE on disease detection, prevention, and treatment	
Conduct large population-based studies to explore biological and environmental underpinnings of VTE along with their patient-oriented nonthrombotic outcomes (highlighted in the Data Supplement)	
Perform population-based studies to examine patient-centered outcomes, including long-term symptoms, functional status, and the consequent effects on quality of life	
Define the impact of VTE on economic and health status measures across different populations	
Determine the effect of healthcare delivery on the variation in VTE outcomes	

DOAC indicates direct oral anticoagulant; DVT, deep vein thrombosis; PE, pulmonary embolism; and VTE, venous thromboembolism.

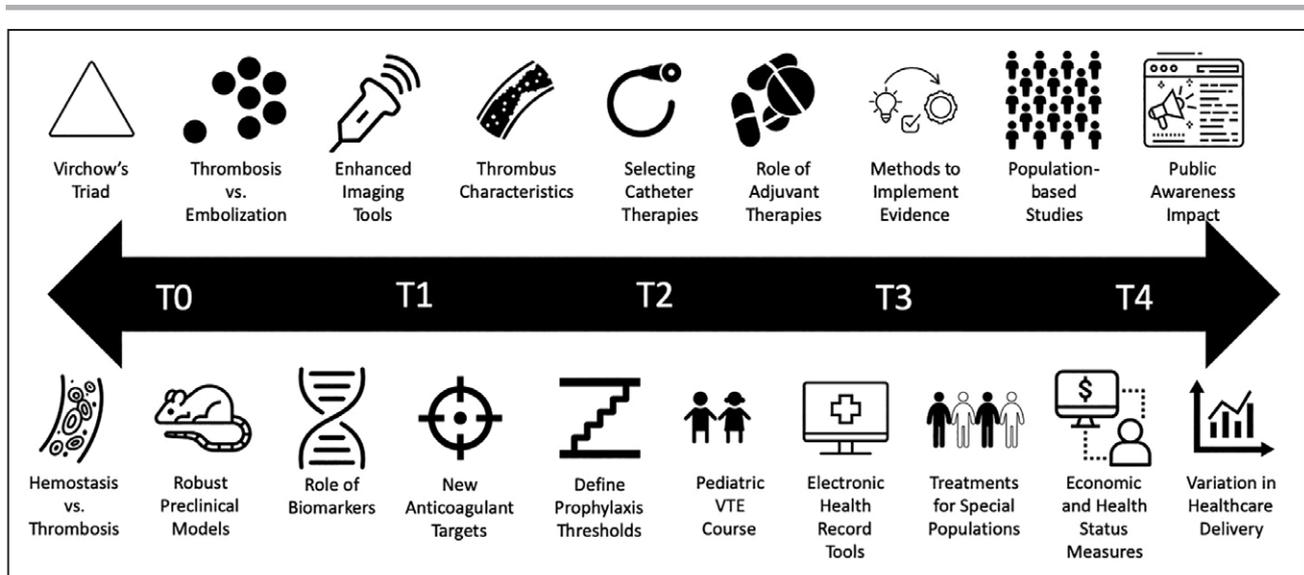


Figure. Priorities for future VTE research across the spectrum of translational research.

T0 indicates fundamental and discovery-based research; T1, human level research; T2, patient level research; T3, practice level research; T4, community and population level research; and VTE, venous thromboembolism.

T0—FUNDAMENTAL RESEARCH: FROM MOLECULES TO BIOLOGICAL SYSTEMS

Most of the time, the coagulation system remains well balanced to respond to vascular injury without clotting within the vessels (hemostasis). However, when clot formation does occur within blood vessels (thrombosis), effects are life-threatening. Mechanisms that differentiate clot formation occurring in the setting of hemostasis versus those that promote thrombosis remain poorly understood. The fact that up to half of VTE cases lack an identifiable provoking trigger highlights a critical knowledge gap regarding the mechanisms that drive pathological thrombus formation.

A persistent gap in developing new approaches to treat and prevent VTE is inadequate understanding of the underlying pathophysiology. Virchow's triad of abnormalities in blood components, the vessel wall, and blood flow defines our understanding of thrombotic risk and provides a platform for fundamental and discovery-based research into the mechanisms driving VTE. Researchers have largely taken a deconstructive approach focused on each component in isolation to determine its independent contribution to thrombus formation. Although these studies have defined numerous mechanisms regarding blood components and their role in VTE,⁸ effects of vascular wall dysfunction and blood flow on physiological and pathological clot formation are still not well characterized. For example, genetic, biochemical, and animal studies of plasma clotting factors have robustly associated abnormal levels of certain plasma proteins with VTE risk.⁹ However, the fact that many patients with these abnormalities do

not develop VTE indicates that additional, coexisting abnormalities of thrombosis, vessel wall dysfunction, or environmental factors are necessary to promote thrombosis. Understanding the complex interactions within VTE risk factors is a driving need in VTE research.

In VTE, as in any thrombotic disease, pathological cross talk between the vessel wall and blood components is considered a driver of thrombosis. This complex scenario is difficult to reproduce in a laboratory setting. Over the years, the scientific community has recognized the importance of both *in vitro* (eg cell coculture, microfluidic, and computational models) and *in vivo* (eg, vena cava ligation, FeCl₃ injury) preclinical models to understand thrombosis and evaluate potential treatments. All current VTE preclinical models have pros and cons. Understanding these strengths and limitations is imperative when choosing models in the context of a given research question.

Given the strength that *in vivo* models can simultaneously incorporate all 3 arms of Virchow's triad, animal research has become an essential tool in efforts to define pathophysiological mechanisms in VTE and has significantly advanced understanding of cellular and biochemical mechanisms. However, live models have their limitations based on species, size, and life span. These differences can limit their application to the human experience of VTE. For example, most PE models do not replicate the human experience in which a DVT embolizes from the deep veins to the lungs. Instead, they commonly rely on protein infusion locally to incite thrombosis. Development of new models that more closely mimic human pathobiology (including embolism) is a high priority given PE-related mortality and differences in DVT- and PE-specific risk factors.¹⁰

T1—TRANSLATIONAL RESEARCH: FROM ANIMALS TO HUMANS

Significant advances in diagnosing, treating, and preventing VTE depend on translating fundamental and discovery-based research findings to humans (T1 research). A high priority in diagnosis of VTE is elucidating thrombus chronicity or embolic potential with imaging that incorporates information on thrombus pathophysiology. This might improve diagnostic accuracy and influence treatment decisions. For example, a lower-extremity thrombus with imaging characteristics that suggest low embolic potential can be safely treated with shorter courses of anticoagulation, whereas one with higher embolic potential might warrant longer courses of anticoagulation or the placement of an inferior vena cava filter if anticoagulation is contraindicated.

The emergence of direct oral anticoagulants has transformed VTE treatment; however, the search continues for even safer treatments.¹¹ Recent epidemiological studies and animal models show relationships between a number of clotting factors (eg, factor XIa, factor XII, and factor IX) and VTE susceptibility. For example, factor XIa inhibition is emerging as a promising therapeutic strategy, with the potential of limited bleeding complications.¹² While various factor inhibitor agents move through the clinical trials pipeline, carefully designed studies should concurrently identify optimal treatment strategies based on patient and VTE characteristics.

Independent of therapy choice, identifying patients at greatest risk for recurrent VTE, who might benefit from long-term secondary prevention, remains a challenge.⁶ Research on defining treatment duration that extends beyond consideration of presenting characteristics (eg, provoked versus unprovoked VTE) is warranted. Significant progress in this area may be possible using innovative imaging and biomarker assessments. Biomarkers other than D-dimer that predict VTE recurrence risk are needed; candidates include soluble P-selectin, factor VIII, factor IX, extracellular DNA, and intercellular adhesion molecule-1, but new biomarkers should be sought.^{13,14} High-resolution imaging and proteomic analysis of thrombi could provide new mechanistic biomarkers of recurrence.¹⁵ Other avenues to pursue include genetic screening, which is complicated by epigenetic factors that also contribute to disease.¹⁶ Unbiased “-omics” approaches that measure circulating microRNAs have identified candidates that are associated with VTE recurrence.¹⁷ Metabolic screening has also shown potential to identify new biomarkers that influence VTE.^{18,19} In sum, personalized approaches to treatment that integrate thrombus pathophysiology, circulating biomarkers, patient characteristics, and patient preferences require study.²⁰

T2—CLINICAL RESEARCH: FROM HUMANS TO PATIENTS

Clinicians struggle to translate findings from discovery-based research to care of individual patients (T2 research). For example, selecting therapies based on VTE recurrence risk remains a largely unfulfilled goal. As noted above, the use of new biomarkers could offer personalization opportunities in VTE treatment. However, challenges remain in translating the findings from T0 and T1 research to large cohorts that can account for the heterogeneity in populations while assessing whether specific therapies influence clot structure in a manner that impacts clinical outcome.²¹

Catheter-based therapies, including thrombolysis, are increasingly used for patients with acute PE or DVT. A way to determine the patients most likely to benefit from an invasive procedure is needed.²² At the same time, clinical, biomarker, and echocardiographic parameter collection (in PE) is necessary for prospective validation of many different risk stratification tools.

The impact of therapy on long-term outcomes is not well described. For example, although pharmacomechanical thrombolysis might not prevent PTS after proximal DVT in general, efficacy in selected patients based on anatomic presentation and persistence of symptoms despite anticoagulation is unknown. The same is true for use of catheter-based therapies in patients with intermediate- and high-risk PE to prevent chronic dyspnea and fatigue associated with the so-called post-PE syndrome.

Few modalities have demonstrated benefit in preventing PTS in patients with DVT. Specifically, compression stockings failed to prevent PTS in at least 1 large randomized study.²³ However, other treatments to prevent PTS merit study, including different anticoagulant strategies, P2Y12 inhibitors, adhesion molecule inhibitors, venoactive drugs, and statins. Finally, limited research is available on effective treatment of PTS, including the roles of the above medications and venous surgical interventions.

Optimizing VTE prevention in hospitalized medical and surgical patients can reduce the population burden of VTE. Several questions require research: identification of patients at highest risk of VTE and bleeding to guide prophylaxis type and duration; understanding why breakthrough VTE occurs in hospitalized patients receiving prophylaxis; identification of methods to enhance compliance with prophylaxis^{24,25}; and methods to reduce overuse of prophylaxis, which is both costly and potentially dangerous. Studies of deimplementation that reduces overuse of therapies (eg, VTE prophylaxis in low-risk patients) are equally important.

Finally, management of VTE in pediatric and pregnant patients remains understudied. The incidence of VTE in pediatric patients is low.²⁶ Harnessing a multicenter consortium to pool standardized anatomic, therapeutic, and

demographic data with long-term follow-up could further define the clinical course of VTE in children. VTE in pregnancy is a highly morbid complication. Although low-molecular-weight heparin is standard of care for prophylaxis in high-risk women, major gaps remain in assessing the absolute VTE risk, selecting the dose, and determining the duration of prophylaxis,^{27,28} as well as in determining the optimal treatment when VTE occurs in pregnant women.

T3—TRANSLATIONAL RESEARCH: FROM PATIENTS TO CLINICAL PRACTICE

Although large-scale clinical trials can establish the efficacy of various interventions (both prophylactic and treatment), implementing these into clinical practice (T3 research) remains a barrier to improved health. Important aspects of evidence-to-practice translation are both the overuse and underuse of treatments. Examples of overuse include placement of inferior vena cava filters for primary prophylaxis in patients at risk for VTE and use of catheter-directed thrombolysis to treat patients with intermediate- and high-risk PE without randomized trial evidence supporting mortality benefits.^{29–31} Examples of underuse include differential prescribing of direct oral anticoagulants and low use of outpatient DVT treatment based on race and socioeconomic factors.^{32,33} Tools (eg, prediction models) are needed to help clinicians select patients most likely to benefit from specific interventions. Integrating these into the electronic medical record could improve safe medication delivery. Additionally, identification of strategies aimed at changing clinician behavior to adopt evidence-based practices is critically important.

The rapid growth in use of devices (eg, vena cava filters, venous stents, thrombolysis and thrombectomy catheters) to treat patients with VTE presents a clinical dilemma. Devices often achieve regulatory approval based largely on safety profile, although randomized controlled trials comparing these devices to noninterventional approaches and between different devices are needed to determine clinical efficacy. Also, postmarketing assessment of device utilization, efficacy, and safety is needed. Well-designed population-based registries can play a role in determining the profile of patients in whom these devices are being used, what clinical benefits can be expected, which patients are more likely to experience benefit, and what risks are associated with use of the devices outside of research settings.

Although each of the direct oral anticoagulants has undergone large-scale trials, some populations were inadequately represented, and race/ethnicity of trial participants was not always diverse. Notable examples of other under-represented groups include patients with severe renal impairment or receiving hemodialysis,

those at extremes of weight, those with reduced absorption because of gastrointestinal surgery, those with autoimmune diseases, and those who have had venous stenting procedures.^{34,35} High-quality efficacy and safety data for direct oral anticoagulant use in cerebral and portal venous thrombosis are also lacking. Because it is impractical to conduct randomized trials in each of these patient groups, observational studies are needed to further assess safety and efficacy.

Finally, many inherited and acquired thrombophilias can be diagnosed in patients with VTE, and some of these increase risk of recurrence after a first event. However, only D-dimer has been adequately studied for guiding management decisions, and little is known on the overall health impact and economics of thrombophilia testing, both in patients and their relatives. More work is needed to understand the benefits and harms of genetic and nongenetic thrombophilia testing and how best to integrate that information into management and prevention.

Across a range of treatment modalities, better equipping of physicians and healthcare systems to translate evidence into practice is needed. This includes identifying subpopulations most likely to benefit from therapies, exploring therapeutic benefits in populations not typically included in randomized trials, and understanding the impact of diagnostic testing on care at the practice and population levels for patients with VTE.

T4—GLOBAL RESEARCH: FROM CLINICAL PRACTICE TO HEALTHCARE SYSTEMS

Public awareness and public health efforts to address VTE prevention and treatment have a limited evidence base (T4 research). Despite VTE being a common disease, few in the public are aware of its signs, symptoms, and risk factors.³⁶ Campaigns such as World Thrombosis Day, initiatives from the American Heart Association, and other efforts may increase awareness, but more studies are needed to gauge improvement in public knowledge based on these programs.

Analogous to research efforts in atherosclerosis, large population-based epidemiology studies are needed to better understand the biological and environmental causes of VTE, as well as the range of nonthrombotic outcomes in patients who have experienced VTE (described in the [Data Supplement](#)). Data from these studies could generate hypotheses on causal mechanisms of VTE and be harnessed to design clinical trials of preventive and therapeutic treatments that precisely target genetic, molecular, clinical, and environmental mechanisms associated with VTE and its recurrence. These studies would include collection of blood and tissue samples for storage in biorepositories for subsequent analysis. Information ranging from genomics,

transcriptomics, proteomics, and metabolomics would be integrated with demographic, clinical, laboratory, and imaging information, as well as exposures (including socioeconomic and other environmental characteristics), to create large databases that could be shared. Outcomes after VTE for conditions that share risk factors with VTE (eg, kidney disease) and psychosocial outcomes after VTE (eg, depression) are poorly understood.

Up to 50% of patients develop long-term exercise limitation after PE or develop PTS after DVT,^{37,38} yet the effect of DVT and PE on long-term health status and societal impacts for many of those who have experienced PE or DVT is not well established. More population-based studies are needed to examine patient-centered outcomes, including long-term symptoms, functional status, and consequent effects on quality of life.³⁹ These studies should use or develop disease-specific measures whenever possible.^{37,40–42} Furthermore, studies are needed to determine best methods for integrating traditional methods of collecting patient-reported quality of life outcomes along with digital health tools, such as wearable sensors, smartphones, and point-of-care devices that monitor biometrics.^{43,44}

Population-based studies are needed to determine the effect of healthcare delivery on VTE outcomes. These include comparative effectiveness studies assessing clinical and economic end points and studies addressing implementation of evidence-based practices (eg, VTE risk assessment and prophylaxis in hospitalized patients). Given the well-documented disparities in health and health care in minority populations in the United States, the latter related to access and outcomes, special attention should be afforded to those populations to address specific predilections and outcomes in those with VTE. This research could involve analysis of data from electronic health records, observational registries, and insurance and administrative claims databases, which would enable assessment of how nonclinical factors such as education, income, insurance coverage and payment policies, and governmental regulations influence diffusion and uptake of effective therapies to affect mortality and morbidity from VTE, as well as the quality of life of patients affected by VTE.⁴⁵ There is an unmet need to define and study similar disparities in other countries.

IMPORTANCE OF INTERDISCIPLINARY APPROACHES

The VTE research field needs answers, and the answers cannot come from one single research tool. Collaboration among experts in each preclinical and clinical area will provide optimal insight to the field and to the patients, the ultimate beneficiaries of our daily efforts.

We propose multidisciplinary approaches that integrate epidemiological, genomic, cellular, biochemical, and biophysical strategies to advance fundamental understanding and translate knowledge to patient care.

Practical methods to study multiple risk factors in concert lag, in part from the complexity of investigations involving multidisciplinary concepts. These studies often require harmonization of complicated and field-specific language to describe technically challenging methods and detailed findings. However, efforts to bridge these gaps and strengthen collaborations are likely to yield new information on pathophysiological mechanisms. For example, a recent approach to combine *in vivo* and *in vitro* analyses with computational modeling and bioengineered microfluidic chambers revealed effects of elevated hematocrit on platelet accumulation within thrombi that were not appreciable in mouse models alone, demonstrating the power of interdisciplinary collaborations.⁴⁶ Accordingly, additional multidisciplinary studies to elucidate mechanisms in VTE are warranted. Devices permitting control of fluid mechanics could enable more controlled studies of the contribution of blood flow than is possible in mice. Studies using biologically engineered “blood vessels” with innovative designs could expose vascular responses to changes in flow, as well as interactions between blood cells and proteins with the vessel wall during DVT.⁴⁷ Similarly, integrating approaches in genomics and epidemiology with functional analysis of molecular mechanisms could define additional pathways that contribute to VTE. This kind of integrated approach might alleviate confounding “noise” in genetic analysis and provide specific and focused hypotheses to guide biological and biochemical studies in new directions. Pathways identified and characterized through these collaborations could provide robust new therapeutic targets and translate genetic discovery to practical applications in the clinic. Facilitating multidisciplinary science teams via specific funding mechanisms is a major priority for advancing in VTE research.

BARRIERS AND OPPORTUNITIES

To solve the problems outlined above, we need to bring together scientists and clinicians from disparate disciplines, including those not traditionally involved in VTE research. For example, at the intersection of rehabilitation science, epidemiology, clinical investigation, health services research, and big data sits an opportunity to explore the prevalence, impact, and potential therapies of the post-PE syndrome.

Although progress is being made in prevention and treatment of cancer-associated VTE, many questions across the translational spectrum remain. These include mechanistic, preventative, and therapeutic questions

about this high-mortality condition. Multidisciplinary teams could use different approaches to better understand the causes, prevention, and treatment of cancer-associated VTE as a distinct entity from non-cancer-associated VTE.

The broad adoption of electronic health records presents an opportunity to gather large quantities of data for retrospective analysis and to screen for patient enrollment in research studies. However, without improvements in quality and availability of natural language processing in electronic health records, much of the data stored is not easily searchable, which presents a major barrier to innovation. Additionally, challenges with interoperability between health systems and electronic health record platforms stifle potential large-scale studies and collaborative efforts.

CONCLUSIONS

Because VTE is a leading cause of death and disability, efforts to improve its prevention, diagnosis, and management are vitally important. Across the spectrum of translational research, opportunities exist to transform the care of patients with VTE. New scientists who become invigorated to explore these high-need areas will have tremendous impact on the population's health. It is imperative that funding agencies and training programs support the next generation of scientists who will solve many of these pressing public health problems.

Disclosures

Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
Mary Cushman	University of Vermont The Robert Larner, M.D. College of Medicine, Burlington, VT, USA	None	None	None	None	None	None	None
Geoffrey D. Barnes	Frankel Cardiovascular Center, University of Michigan, Ann Arbor, MI, USA	AHRQ†; Blue Cross Blue Shield of Michigan†; NHLBI†; Pfizer/Bristol- Myers Squibb†	None	None	None	None	AMAG Pharmaceuticals*; Janssen*; Pfizer/ Bristol-Myers Squibb*; Portola*	None
Mark A. Creager	Heart and Vascular Center, Dartmouth- Hitchcock Medical Center, Geisel School of Medicine at Dartmouth, Hanover, NH, USA	American Heart Association (AHA Vascular Disease SFRN)*	None	None	None	None	None	None
Jose A. Diaz	Division of Surgical Research, Vanderbilt University Medical Center, Nashville, TN, USA	None	None	None	None	None	None	None

(Continued)

ARTICLE INFORMATION

The American Heart Association and the International Society on Thrombosis and Haemostasis make 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.

This document was approved by the American Heart Association Science Advisory and Coordinating Committee on April 27, 2020; the American Heart Association Executive Committee on June 22, 2020; and by the International Society on Thrombosis and Haemostasis on April 27, 2020.

Data Supplements are available with this article at <https://www.ahajournals.org/doi/suppl/10.1161/CIR.0000000000000818>.

The American Heart Association requests that this document be cited as follows: Cushman M, Barnes GD, Creager MA, Diaz JA, Henke PK, Machlus KR, Nieman MT, Wolberg AS; on behalf of the American Heart Association Council on Peripheral Vascular Disease; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Epidemiology and Prevention; and the International Society on Thrombosis and Haemostasis. Venous thromboembolism research priorities: a scientific statement from the American Heart Association and the International Society on Thrombosis and Haemostasis. *Circulation*. 2020;141:e000000000000818. doi: 10.1161/CIR.0000000000000818.

This article has been copublished in *Research and Practice in Thrombosis and Haemostasis*.

Copies: This document is available on the websites of the American Heart Association (professional.heart.org) and the International Society on Thrombosis and Haemostasis (<https://www.isth.org/>). A copy of the document is available at <https://professional.heart.org/statements> by using either "Search for Guidelines & Statements" or the "Browse by Topic" area. To purchase additional reprints, call 215-356-2721 or email Meredith.Edelman@wolterskluwer.com.

The expert peer review of AHA-commissioned documents (eg, scientific statements, clinical practice guidelines, systematic reviews) is conducted by the AHA Office of Science Operations. For more on AHA statements and guidelines development, visit <https://professional.heart.org/statements>. Select the "Guidelines & Statements" drop-down menu, then click "Publication Development."

Permissions: Multiple copies, modification, alteration, enhancement, and/or distribution of this document are not permitted without the express permission of the American Heart Association. Instructions for obtaining permission are located at <https://www.heart.org/permissions>. A link to the "Copyright Permissions Request Form" appears in the second paragraph (<https://www.heart.org/en/about-us/statements-and-policies/copyright-request-form>).

Writing Group Disclosures Continued

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
Peter K. Henke	Department of Surgery, University of Michigan, Ann Arbor, MI, USA	None	None	None	None	None	None	None
Kellie R. Machlus	Department of Medicine, Harvard Medical School, Brigham and Women's Hospital, Boston, MA, USA	None	None	None	None	None	None	None
Marvin T. Nieman	Department of Pharmacology, Case Western Reserve University, Cleveland, OH, USA	NIH (PI on an NIH grant)†	None	None	None	None	None	None
Alisa S. Wolberg	Department of Pathology and Laboratory Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA	Novo Nordisk†; BMS†; Shire† (all research funding)	None	None	None	None	BPL*	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.



Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
Marc Carrier	University of Ottawa (Canada)	BMS (Apixaban and placebo)†; Leo Pharma (Tinzaparin)†; Pfizer (Dalteparin and operational funding)†	None	Bayer*; BMS*; Servier*; Pfizer*	None	None	BMS*; Bayer*; Servier*	None
Naomi M. Hamburg	Boston University	None	None	None	None	None	Merck*; Bayer*; Sanifit*	None
Susan R. Kahn	McGill University (Canada)	None	None	None	None	None	None	None
Jeffrey I. Weitz	Thrombosis & Atherosclerosis Research Institute (Canada)	None	None	Bayer†; Boehringer Ingelheim†; Bristol Myers Squibb†; Daiichi-Sankyo†; Ionis†; Janssen†; Novartis†; Merck†; Pfizer†; Portola†	None	None	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

REFERENCES

- Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Das SR, et al; on behalf of the American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2019 update: a report from the American Heart Association [published correction appears in *Circulation*. 2020;141:e33]. *Circulation*. 2019;139:e56–e528. doi: 10.1161/CIR.0000000000000659
- ISTH Steering Committee for World Thrombosis Day. Thrombosis: a major contributor to the global disease burden. *J Thromb Haemost*. 2014;12:1580–1590. doi: 10.1111/jth.12698

3. Bell EJ, Lutsey PL, Basu S, Cushman M, Heckbert SR, Lloyd-Jones DM, Folsom AR. Lifetime risk of venous thromboembolism in two cohort studies. *Am J Med*. 2016;129:339.e19–339.e26. doi: 10.1016/j.amjmed.2015.10.014
4. Søgaard KK, Schmidt M, Pedersen L, Horváth-Puhó E, Sørensen HT. 30-year mortality after venous thromboembolism: a population-based cohort study. *Circulation*. 2014;130:829–836. doi: 10.1161/CIRCULATIONAHA.114.009107
5. Rabinovich A, Kahn SR. The postthrombotic syndrome: current evidence and future challenges. *J Thromb Haemost*. 2017;15:230–241. doi: 10.1111/jth.13569
6. *The Surgeon General's Call to Action to Prevent Deep Vein Thrombosis and Pulmonary Embolism*. Rockville, MD: Office of the Surgeon General (US), National Heart, Lung, and Blood Institute; 2008.
7. Creager MA, Beckman JA, Conte MS, Cushman M, Faxon DP, Hiatt WR, Hirsch AT, McDermott MM, Bonaca MP, Collins T, et al. American Heart Association. Improving Vascular Disease Prevention, Detection and Treatment. https://professional.heart.org/idc/groups/ahamh-public/@wcm/@sop/@scon/documents/downloadable/ucm_478975.pdf. Accessed September 22, 2019.
8. Wolberg AS, Aleman MM, Leiderman K, Machlus KR. Procoagulant activity in hemostasis and thrombosis: Virchow's triad revisited. *Anesth Analg*. 2012;114:275–285. doi: 10.1213/ANE.0b013e31823a088c
9. Wolberg AS, Rosendaal FR, Weitz JI, Jaffer IH, Agnelli G, Baglin T, Mackman N. Venous thrombosis. *Nat Rev Dis Primers*. 2015;1:15006. doi: 10.1038/nrdp.2015.6
10. van Langevelde K, Flinterman LE, van Hylckama Vlieg A, Rosendaal FR, Cannegieter SC. Broadening the factor V Leiden paradox: pulmonary embolism and deep-vein thrombosis as 2 sides of the spectrum. *Blood*. 2012;120:933–946. doi: 10.1182/blood-2012-02-407551
11. Weitz JI, Fredenburgh JC. Factors XI and XII as targets for new anticoagulants. *Front Med (Lausanne)*. 2017;4:19. doi: 10.3389/fmed.2017.00019
12. Quan ML, Pinto DJ, Smallheer JM, Ewing WR, Rossi KA, Luetgten JM, Seiffert DA, Wexler RR. Factor XIa inhibitors as new anticoagulants. *J Med Chem*. 2018;61:7425–7447. doi: 10.1021/acs.jmedchem.8b00173
13. Jacobs B, Obi A, Wakefield T. Diagnostic biomarkers in venous thromboembolic disease. *J Vasc Surg Venous Lymphat Disord*. 2016;4:508–517. doi: 10.1016/j.jvs.2016.02.005
14. Rabinovich A, Cohen JM, Prandoni P, Kahn SR. Association between thrombophilia and the post-thrombotic syndrome: a systematic review and meta-analysis. *J Thromb Haemost*. 2014;12:14–23. doi: 10.1111/jth.12447
15. Stachowicz A, Siudut J, Suski M, Olszanecki R, Korbut R, Undas A, Wiśniewski JR. Optimization of quantitative proteomic analysis of clots generated from plasma of patients with venous thromboembolism. *Clin Proteomics*. 2017;14:38. doi: 10.1186/s12014-017-9173-x
16. Benincasa G, Costa D, Infante T, Lucchese R, Donatelli F, Napoli C. Interplay between genetics and epigenetics in modulating the risk of venous thromboembolism: a new challenge for personalized therapy. *Thromb Res*. 2019;177:145–153. doi: 10.1016/j.thromres.2019.03.008
17. Wang X, Sundquist S, Svensson PJ, Rastkhani H, Palmér K, Memon AA, Sundquist J, Zöller B. Association of recurrent venous thromboembolism and circulating microRNAs. *Clin Epigenetics*. 2019;11:28. doi: 10.1186/s13148-019-0627-z
18. Goldenberg NA, Everett AD, Graham D, Bernard TJ, Nowak-Göttl U. Proteomic and other mass spectrometry based “omics” biomarker discovery and validation in pediatric venous thromboembolism and arterial ischemic stroke: current state, unmet needs, and future directions. *Proteomics Clin Appl*. 2014;8:828–836. doi: 10.1002/prca.201400062
19. Deguchi H, Banerjee Y, Trauger S, Siuzdak G, Kalisiak E, Fernández JA, Hoang L, Tran M, Yegneswaran S, Elias DJ, et al. Acylcarnitines are anticoagulants that inhibit factor Xa and are reduced in venous thrombosis, based on metabolomics data. *Blood*. 2015;126:1595–1600. doi: 10.1182/blood-2015-03-636761
20. Wolberg AS, Mackman N. Venous thromboembolism: risk factors, biomarkers, and treatment. *Arterioscler Thromb Vasc Biol*. 2009;29:296–297. doi: 10.1161/ATVBAHA.109.184580
21. Janion-Sadowska A, Natorska J, Siudut J, Ząbczyk M, Stanis A, Undas A. Plasma fibrin clot properties in the G20210A prothrombin mutation carriers following venous thromboembolism: the effect of rivaroxaban. *Thromb Haemost*. 2017;117:1739–1749. doi: 10.1160/TH17-01-0060
22. Chatterjee S, Chakraborty A, Weinberg I, Kadakia M, Wilensky RL, Sardar P, Kumbhani DJ, Mukherjee D, Jaff MR, Giri J. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. *JAMA*. 2014;311:2414–2421. doi: 10.1001/jama.2014.5990
23. Kahn SR, Shapiro S, Wells PS, Rodger MA, Kovacs MJ, Anderson DR, Tagalakis V, Houweling AH, Ducruet T, Holcroft C, et al; SOX Trial Investigators. Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial. *Lancet*. 2014;383:880–888. doi: 10.1016/S0140-6736(13)61902-9
24. Lau BD, Streiff MB, Pronovost PJ, Haut ER. Venous thromboembolism quality measures fail to accurately measure quality. *Circulation*. 2018;137:1278–1284. doi: 10.1161/CIRCULATIONAHA.116.026897
25. Schünemann HJ, Cushman M, Burnett AE, Kahn SR, Beyer-Westendorf J, Spencer FA, Rezzato SM, Zakai NA, Bauer KA, Dentali F, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. *Blood Adv*. 2018;2:3198–3225. doi: 10.1182/bloodadvances.2018022954
26. Thompson AJ, McSwain SD, Webb SA, Stroud MA, Streck CJ. Venous thromboembolism prophylaxis in the pediatric trauma population. *J Pediatr Surg*. 2013;48:1413–1421. doi: 10.1016/j.jpedsurg.2013.02.059
27. Bates SM, Rajasekhar A, Middeldorp S, McLintock C, Rodger MA, James AH, Vazquez SR, Greer IA, Riva JJ, Bhatt M, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy. *Blood Adv*. 2018;2:3317–3359. doi: 10.1182/bloodadvances.2018024802
28. Ward CM, Andrews RK; ISTH State of the Art Speakers. Illustrated state-of-the-art capsules of the ISTH 2019 Congress in Melbourne, Australia. *Res Pract Thromb Haemost*. 2019;3:431–497. doi: 10.1002/rth2.12225
29. Bickdeli B, Chatterjee S, Desai NR, Kirtane AJ, Desai MM, Bracken MB, Spencer FA, Monreal M, Goldhaber SZ, Krumholz HM. Inferior vena cava filters to prevent pulmonary embolism: systematic review and meta-analysis. *J Am Coll Cardiol*. 2017;70:1587–1597. doi: 10.1016/j.jacc.2017.07.775
30. Kucher N, Boekstegers P, Müller OJ, Kupatt C, Beyer-Westendorf J, Heitzer T, Tebbe U, Horstkotte J, Müller R, Blessing E, et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. *Circulation*. 2014;129:479–486. doi: 10.1161/CIRCULATIONAHA.113.005544
31. Gayou EL, Makary MS, Hughes DR, Hemingway J, Elliott ED, Spain JW, Prevedello LM. Nationwide trends in use of catheter-directed therapy for treatment of pulmonary embolism in Medicare beneficiaries from 2004 to 2016. *J Vasc Interv Radiol*. 2019;30:801–806. doi: 10.1016/j.jvir.2019.02.024
32. Nathan AS, Geng Z, Dayoub EJ, Khatana SAM, Eberly LA, Kobayashi T, Pugliese SC, Adusumalli S, Giri J, Groeneveld PW. Racial, ethnic, and socioeconomic inequities in the prescription of direct oral anticoagulants in patients with venous thromboembolism in the United States. *Circ Cardiovasc Qual Outcomes*. 2019;12:e005600. doi: 10.1161/CIRCOUTCOMES.119.005600
33. Douce D, McClure LA, Lutsey P, Cushman M, Zakai NA. Outpatient treatment of deep vein thrombosis in the United States: the Reasons for Geographic and Racial Differences in Stroke Study. *J Hosp Med*. 2017;12:826–830. doi: 10.12788/jhm.2831
34. Moll S, Crona DJ, Martin K. Direct oral anticoagulants in extremely obese patients: OK to use? *Res Pract Thromb Haemost*. 2019;3:152–155. doi: 10.1002/rth2.12178
35. Padmos LJ, Garcia D. May-Thurner syndrome and thrombosis: a systematic review of antithrombotic use after endovascular stent placement. *Res Pract Thromb Haemost*. 2019;3:70–78. doi: 10.1002/rth2.12156
36. Wendelboe AM, McCumber M, Hylek EM, Buller H, Weitz JI, Raskob G; ISTH Steering Committee for World Thrombosis Day. Global public awareness of venous thromboembolism. *J Thromb Haemost*. 2015;13:1365–1371. doi: 10.1111/jth.13031
37. Kahn SR, Hirsch AM, Akaberi A, Hernandez P, Anderson DR, Wells PS, Rodger MA, Solymoss S, Kovacs MJ, Rudski L, et al. Functional and exercise limitations after a first episode of pulmonary embolism: results of the ELOPE Prospective Cohort Study. *Chest*. 2017;151:1058–1068. doi: 10.1016/j.chest.2016.11.030
38. Ten Cate-Hoek AJ. Prevention and treatment of the post-thrombotic syndrome. *Res Pract Thromb Haemost*. 2018;2:209–219. doi: 10.1002/rth2.12085
39. Rumsfeld JS, Alexander KP, Goff DC Jr, Graham MM, Ho PM, Masoudi FA, Moser DK, Roger VL, Slaughter MS, Smolderen KG, et al; on behalf of

the American Heart Association Council on Quality of Care and Outcomes Research, Council on Cardiovascular and Stroke Nursing, Council on Epidemiology and Prevention, Council on Peripheral Vascular Disease, and Stroke Council. Cardiovascular health: the importance of measuring patient-reported health status: a scientific statement from the American Heart Association. *Circulation*. 2013;127:2233–2249. doi: 10.1161/CIR.0b013e3182949a2e

40. Klok FA, Cohn DM, Middeldorp S, Scharloo M, Büller HR, van Kralingen KW, Kaptein AA, Huisman MV. Quality of life after pulmonary embolism: validation of the PEEmb-QoL Questionnaire. *J Thromb Haemost*. 2010;8:523–532. doi: 10.1111/j.1538-7836.2009.03726.x
41. Kahn SR, Lamping DL, Ducruet T, Arsenault L, Miron MJ, Roussin A, Desmarais S, Joyal F, Kassis J, Solymoss S, et al; VETO Study Investigators. VEINES-QOL/Sym questionnaire was a reliable and valid disease-specific quality of life measure for deep venous thrombosis [published correction appears in *J Clin Epidemiol*. 2006;59:1334]. *J Clin Epidemiol*. 2006;59:1049–1056. doi: 10.1016/j.jclinepi.2005.10.016
42. Ghanima W, Wik HS, Tavoly M, Enden T, Jelsness-Jørgensen LP. Late consequences of venous thromboembolism: measuring quality of life after deep vein thrombosis and pulmonary embolism. *Thromb Res*. 2018;164:170–176. doi: 10.1016/j.thromres.2017.07.025
43. McConnell MV, Shcherbina A, Pavlovic A, Homburger JR, Goldfeder RL, Waggot D, Cho MK, Rosenberger ME, Haskell WL, Myers J, et al. Feasibility of obtaining measures of lifestyle from a smartphone app: the MyHeart Counts Cardiovascular Health Study. *JAMA Cardiol*. 2017;2:67–76. doi: 10.1001/jamacardio.2016.4395
44. Topol EJ. A decade of digital medicine innovation. *Sci Transl Med*. 2019;11:eaaw7610. doi: 10.1126/scitranslmed.aaw7610
45. Maddox TM, Albert NM, Borden WB, Curtis LH, Ferguson TB Jr, Kao DP, Marcus GM, Peterson ED, Redberg R, Rumsfeld JS, et al; on behalf of the American Heart Association Council on Quality of Care and Outcomes Research; Council on Cardiovascular Disease in the Young; Council on Clinical Cardiology; Council on Functional Genomics and Translational Biology; and Stroke Council. The learning health-care system and cardiovascular care: a scientific statement from the American Heart Association. *Circulation*. 2017;135:e826–e857. doi: 10.1161/CIR.0000000000000480
46. Walton BL, Lehmann M, Skorzewski T, Holle LA, Beckman JD, Cribb JA, Mooberry MJ, Wufsus AR, Cooley BC, Homeister JW, et al. Elevated hematocrit enhances platelet accumulation following vascular injury. *Blood*. 2017;129:2537–2546. doi: 10.1182/blood-2016-10-746479
47. Tsai M, Kita A, Leach J, Rounsevell R, Huang JN, Moake J, Ware RE, Fletcher DA, Lam WA. In vitro modeling of the microvascular occlusion and thrombosis that occur in hematologic diseases using microfluidic technology. *J Clin Invest*. 2012;122:408–418. doi: 10.1172/JCI58753



Circulation