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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 (pending)

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Abstract

Venous thromboembolism is a major cause of morbidity and mortality. The impact of the Surgeon General's Call to Action in 2008 has been lower than expecated 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 pathobiologic causative mechanisms for the 50% of patients with unprovoked venous thromboembolism and a 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 (e.g., 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 biologic and environmental underpinings 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.

Essentials:

- The is statement presents future research priorities in venous thromboembolism
- It was developed by experts and a crowdsourcing survey across 16 scientific organizations
- It covers fundamental (T0), clinical (T1), practice level (T2), and community and population level (T4) research.
- Authors suggest multidisciplinary team science approaches be prioritized

Introduction

Venous thromboembolism (VTE) remains a major cause of morbidity and mortality, affecting up to 1 million Americans and more than 700,000 Europeans annually.[1] Comprised of both deep vein thrombosis (DVT) and pulmonary embolism (PE), VTE disproportionately impacts older adults worldwide.[2] An estimated one-in-twelve people will develop VTE after age 45.[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 post thrombotic syndrome (PTS), which consists of pain, swelling, skin changes, and ulceration; 5-10% will have severe morbidity with reduced quality of life.[5]

In 2008, the United States Surgeon General issued a Call to Action to prevent DVT and PE.[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. While 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 online appendix, in 2018, members of 16 international organizations, including lead organizations for this project (American Heart Association, American Venous Forum, and International Society on Thrombosis and Haemostasis) were invited in a crowdsourcing activity to share their priorities for VTE research through a survey. While attempts were made to include a global perspective, we did not collect participant location and North American participation may be over-represented. 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 upon survey results. The final manuscript 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 has led to pressing need for basic, translational and clinical research, including on antithrombotic treatments in these patients.

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, co-existing 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 (e.g. cell co-culture, microfluidic, and computational models) and in vivo (e.g., vena cava ligation, $FeCl_3$ 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 one or more models in the context of a given research question.

Given the strength that in vivo models can simultaneously incorporate all three arms of Virchow's Triad, animal research has become an essential tool in efforts to define pathophysiologic 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 where a DVT embolizes from the deep veins to the lungs. Instead, they commonly rely on protein infusion locally to incite thrombosis. Developing 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 depends 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 may be safely treated with shorter courses of anticoagulation while one with higher embolic potential may warrant longer courses of anticoagulation or the placement of an inferior vena cava filter if anticoagulation is contraindicated.

The emergence of direct oral anticoagulants (DOACs) 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 cloting factors (e.g. FXIa, FXII, and FIX) and VTE. For example, FXIa 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- charactersitics.

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 (e.g.,

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 may 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 has 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

Clinicans 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 may 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 if 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 and/or DVT. Determining 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, while pharmacomechanical thrombolysis may not prevent PTS after proximal DVT in general, efficacy

in selected patients based on anatomical 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 one 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 de-implementation that reduce overuse of therapies (e.g. VTE prophylaxis in low-risk patients) are equally important.

Finally, management of VTE in pediatric and pregnant patients remains under-studied. 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 may further define the clinical course of VTE in children. VTE in pregnancy is a highly morbid complication. While LMWH is standard of care for prophylaxis in high-risk women, major gaps remain in assessing the absolute VTE risk, selecting dose, and determining duration of prophylaxis, [27, 28] and in optimal treatment when VTE occurs in pregnant women.

T3 – Translational research: from patients to clinical practice

While 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 for treating patients with intermediate- and high-risk PE without randomized trial evidence supporting mortality benefits.[29-31] Examples of underuse include differential DOAC prescribing and low use of outpatient DVT treatment based on race and socioeconomic factors.[32, 33] Tools (e.g., prediction models) are needed to help clinicians select patients most likely to benefit from specific interventions. Integrating these into the electronic medical record may improve safe medication delivery. Additionally, identification of strategies aimed at changing clinician behavior to adopt evidence-based practices are critically important.

The rapid growth in use of devices (e.g., 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, while randomized controlled trials comparing these devices to non-interventional approaches and between different devices are needed to determine clinical efficacy. Also, post-marketing 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 which 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.

While each of the DOACs have undergone large-scale trials, some populations were inadequately represented and race/ethnicity of trial participants was not always diverse. Notable examples include patients with severe renal impairment or receiving hemodialysis, those at extremes of weight, those with reduced absorption due to gastrointestinal surgery , those with autoimmune diseases and those who have had venous stenting procedures.[34, 35] High-quality efficacy and safety data for DOAC use in cerebral and portal venous thrombosis is also lacking. Since 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 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 non-genetic thrombophilia testing and how best to integrate that information into management and prevention.

Across a range of treatment modalities, better equipping physician and health care 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 biologic and environmental causes of VTE, and the range of non-thrombotic outcomes in patients who have experienced VTE (described in supplemental appendix). 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/or 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, imaging information, and 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 (e.g., kidney disease) and psychosocial outcomes after VTE (e.g., depression) are poorly understood.

Up to 50% of patients develop long-term exercise limitation after PE or the PTS following DVT.[37, 38] Yet, the effect of DVT and PE on long term health status and societal impacts for many of those afflicted is not well established. More population-based studies are needed to examine patient centered outcomes, including chronic 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 endpoints, and studies addressing implementation of evidence-based practices (e.g., VTE risk assessment and prophylaxis in hospitalized patients). Given the well-documented disparities in health and healthcare in minority populations in the U.S., 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 non-clinical factors like education, income, insurance coverage and payment policies, and governmental regulations influence diffusion and uptake of effective therapies to affect mortality and morbidity from VTE, and the quality of life of patients affected by VTE.[45]

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 pre-clinical and clinical area will provide optimal insight to the field and to the patients, the ultimately beneficiary of our daily efforts.
We propose multidisciplinary approaches that integrate epidemiologic, 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 pathophysiologic 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 permiting control of fluid mechanics may enable more controlled studies of the contribution of blood flow than is possible in mice. Studies using biologically-engineered "blood vessels" with innovative designs may 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 may define additional pathways that contribute to VTE. This kind of integrated approach may 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 may 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.

While 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 may employ different approaches to better understand the etiology, 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, presenting a major barrier to innovation. Additionally, challenges with interoperability between health systems and electronic health record platforms stifles potential large-scale studies and collaborative efforts.

Conclusion

As a leading cause of death and disability, efforts to improve the prevention, diagnosis, and management of VTE 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 tremenous 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.

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Table – Some Research Priorities in Venous Thromboembolism 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 versus embolization

T1

- 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

- Identify patients most likely to benefit from catheter-based therapies in both PE and proximal DVT
- Explore the role of adjuvant therapies (e.g., statins, P2Y12 inhibitors) to prevent post-thrombotic syndrome
- Select factors for "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

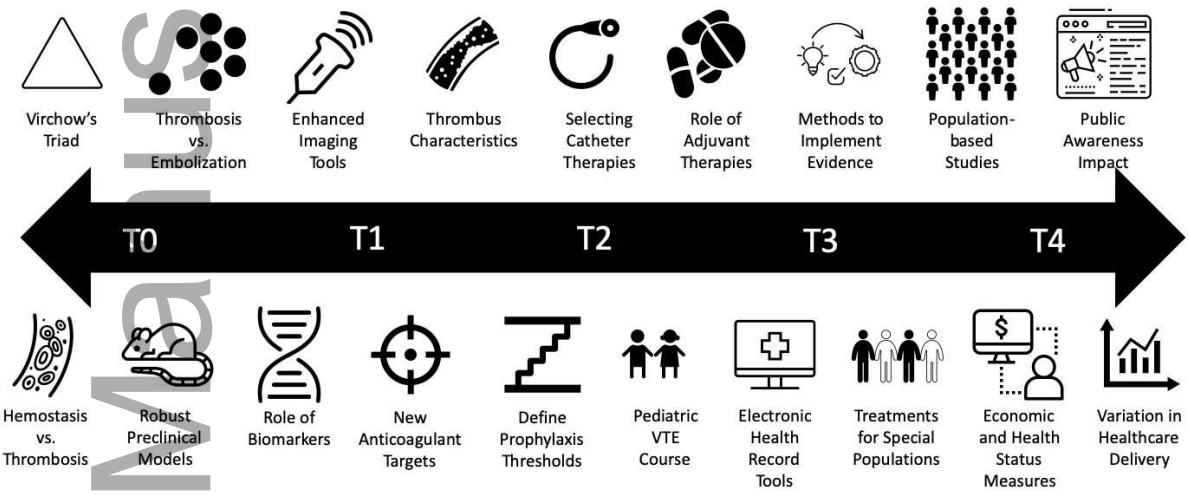
T3

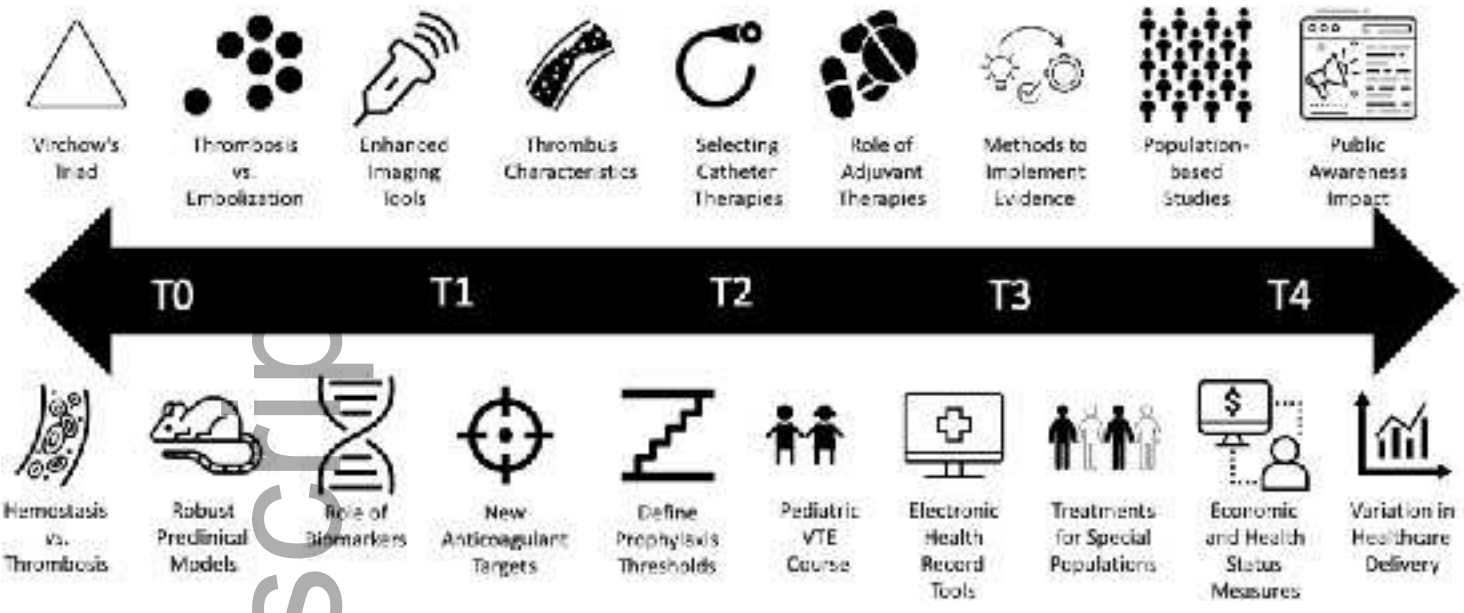
- Study methods to better implement VTE trial evidence into clinical practice, including both overuse and underuse of VTE-specific therapies
- Explore the role of the electronic medical record and population health tools intended to drive appropriate clinical care
- Study effectiveness of devices for PE and DVT treatment (ie. 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 non-clinical impacts of thrombophilia testing in patients, their families, and the population at large

T4

- Assess the impact of public awareness campaigns about VTE on disease detection, prevention, and treatment
- Conduct large population-based studies to explore biologic and environmental underpinnings of VTE along with their patient-oriented non-thrombotic outcomes (highlighted in the supplemental appendix)
- Perform population-based studies to examine patient-centered outcomes, including chronic 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

Central Figure – Priorities in Venous Thromboemnolism Research Across the Translational Spectrum





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