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.
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 morbidty 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 |

| 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 (circuiting factors, genomics, etc) to identify populations most likely to benefit from VTE prophylaxis or treatment |

| 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 |

| 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 |

| 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 |

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

Cushman et al

Venous Thromboembolism Research Priorities

Circulation. 2020;141:00–00. DOI: 10.1161/CIR.0000000000000818

Downloaded from http://ahajournals.org by on July 9, 2020
CLINICAL STATEMENTS AND GUIDELINES

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, 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. 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.
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. Recent epidemiological studies and animal models show relationships between a number of clotting factors (eg, factor Xla, factor XII, and factor IX) and VTE susceptibility. For example, factor Xla inhibition is emerging as a promising therapeutic strategy, with the potential of limited bleeding complications. 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. 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.

High-resolution imaging and proteomic analysis of thrombi could provide new mechanistic biomarkers of recurrence. Other avenues to pursue include genetic screening, which is complicated by epigenetic factors that also contribute to disease. Unbiased “-omics” approaches that measure circulating microRNAs have identified candidates that are associated with VTE recurrence. Metabolic screening has also shown potential to identify new biomarkers that influence VTE. In sum, personalized approaches to treatment that integrate thrombus pathophysiology, circulating biomarkers, patient characteristics, and patient preferences require study.

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.

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. 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 thrombolytic 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. 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, and methods to reduce overseer of prophylaxis, which is both costly and potentially dangerous. Studies of deimplementation that reduces overseer 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. Harnessing a multicenter consortium to pool standardized anatomic, therapeutic, and

Cushman et al Venous Thromboembolism Research Priorities

Circulation. 2020;141:00–00. DOI: 10.1161/CIR.0000000000000818
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, 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. Examples of underuse include differential prescribing of direct oral anticoagulants and low use of outpatient DVT treatment based on race and socioeconomic factors. 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 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. 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. 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, 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. These studies should use or develop disease-specific measures whenever possible. 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 biomarkers.

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. 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. 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. 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 discovery 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 University of Michigan, Ann Arbor, MI, USA | AHRQ; Blue Cross Blue Shield of Michigan; NHLBII; 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)
Cushman et al Venous Thromboembolism Research Priorities

REFERENCES

1. 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 of the American Heart Association [published correction appears in Circulation. 2020;141:e33]. Circulation. 2019;139:e56–e528. doi: 10.1161/CIR.0000000000000659

2. 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, Busu S, Cushman M, Heckbert SR, Lloyd-Jones DM, Folsom AR. Lifetime risk of venous thromboembolism in two cohort studies. *Am J Med*. 2016;132:339.e19–339.e26. doi: 10.1016/j.amjmed.2015.10.014

4. Søgaard KK, Schmidt M, Pedersen L, Horváth-Puhó E, Sørensen H. 30-year mortality after venous thromboembolism: a population-based cohort study. *Circulation*. 2014;130:829–836. doi: 10.1161/CIRCULATIONAHA.114.019107

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, Jenkins TM, Jones CA, Lloyd-Jones DM, et al. American Heart Association. Improving Vascular Disease Prevention, Detection, and Treatment. https://professional.heart.org/idc/groups/ahamah-public/@wcm/@sop/@nla/@rth/@pgjs/@pdf/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*. 2015;121:747–755. doi: 10.1213/ANE.0000000000000818

9. Wolberg AS, Rosendaal FR, Weitz JI, Agnelli G, Baglin T, Jaffer IH, Agnelli G, Baglin T. Procoagulant activity in hemostasis and thrombosis: Virchow's triad revisited. *Anesth Analg*. 2015;121:747–755. doi: 10.1213/ANE.0000000000000818

10. Wolberg AS, Rosendaal FR, Weitz JI, Agnelli G, Baglin T, Jaffer IH, Agnelli G, Baglin T. Procoagulant activity in hemostasis and thrombosis: Virchow's triad revisited. *Anesth Analg*. 2015;121:747–755. doi: 10.1213/ANE.0000000000000818

11. Wolberg AS, Rosendaal FR, Weitz JI, Agnelli G, Baglin T, Jaffer IH, Agnelli G, Baglin T. Procoagulant activity in hemostasis and thrombosis: Virchow's triad revisited. *Anesth Analg*. 2015;121:747–755. doi: 10.1213/ANE.0000000000000818

12. Quan ML, Pinto DJP, Smallheer JM, Ewing WR, Rossi KA, Luettgen JM, Cushman et al Venous Thromboembolism Research Priorities

13. Bell EJ, Lutsey PL, Basu S, Cushman M, Heckbert SR, Lloyd-Jones DM, Creager MA, Beckman JA, Conte MS, Cushman M, Faxon DP, Hiatt WR, Hirsch AT, Jenkins TM, Jones CA, Lloyd-Jones DM, et al. American Heart Association. Improving Vascular Disease Prevention, Detection, and Treatment. https://professional.heart.org/idc/groups/ahamah-public/@wcm/@sop/@nla/@rth/@pgjs/@pdf/documents/downloadable/ucm_478975.pdf. Accessed September 22, 2019.

14. Creager MA, Beckman JA, Conte MS, Cushman M, Faxon DP, Hiatt WR, Hirsch AT, Jenkins TM, Jones CA, Lloyd-Jones DM, et al. American Heart Association. Improving Vascular Disease Prevention, Detection, and Treatment. https://professional.heart.org/idc/groups/ahamah-public/@wcm/@sop/@nla/@rth/@pgjs/@pdf/documents/downloadable/ucm_478975.pdf. Accessed September 22, 2019.

15. Stachowicz A, Siudut J, Suski M, Olszanecki R, Korbut R, Undas A, bczyk M, Stanisz A, Undas A. May-Thurner syndrome and thrombosis: a systematic review and validation in pediatric venous thromboembolism and arterial ischemic syndrome, based on metabolomics data. *Blood Adv*. 2018;2:3317–3359. doi: 10.1182/bloodadvances.2018024802

16. Benincasa G, Costa D, Infante T, Lucchese R, Donatelli F, Napoli C. Inter -...
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.0b013e31829492e

40. Klok FA, Cohn DM, Middelkoop E, Scharloo M, Büller HR, van Kralingen KW, Kaptein AA, Huisman MV. Quality of life after pulmonary embolism: validation of the PEmb-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, 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, Waggon 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:eaaaw7610. 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 healthcare 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, Skorczewski T, Holle LA, Beckman JD, Cribb JA, Mooberry MJ, Wufus 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