Circulation

AHA POLICY STATEMENT

Call to Action to Prevent Venous Thromboembolism in Hospitalized Patients

A Policy Statement From the American Heart Association

ABSTRACT: Venous thromboembolism (VTE) is a major preventable disease that affects hospitalized inpatients. Risk stratification and prophylactic measures have good evidence supporting their use, but multiple reasons exist that prevent full adoption, compliance, and efficacy that may underlie the persistence of VTE over the past several decades. This policy statement provides a focused review of VTE, risk scoring systems, prophylaxis, and tracking methods. From this summary, 5 major areas of policy guidance are presented that the American Heart Association believes will lead to better implementation, tracking, and prevention of VTE events. They include performing VTE risk assessment and reporting the level of VTE risk in all hospitalized patients, integrating preventable VTE as a benchmark for hospital comparison and pay-for-performance programs, supporting appropriations to improve public awareness of VTE, tracking VTE nationwide with the use of standardized definitions, and developing a centralized data steward for data tracking on VTE risk assessment, prophylaxis, and rates.

Peter K. Henke, MD, FAHA, Chair
Susan R. Kahn, MD, MSc, FRCP
Christopher J. Pannucci, MD, MS
Eric A. Secemksy, MD
Natalie S. Evans, MD, FAHA
Alok A. Khorana, MD
Mark A. Creager, MD, FAHA
Aruna D. Pradhan, MD, MPH, FAHA
On behalf of the American Heart Association Advocacy Coordinating Committee

Acute venous thromboembolism (VTE), comprising deep venous thrombosis (DVT) of the legs or pelvis and pulmonary embolism (PE), is a frequent complication in hospitalized patients, a leading contributor to increased length of stay, and the leading cause of preventable hospital death in the United States and worldwide.[1–5] About two-thirds of patients with VTE present with DVT only. The remaining present with PE as the first manifestation and primary cause of VTE-related mortality.[6] Most estimates place the US annual incidence of clinically validated (ie, objectively diagnosed) VTE in adults at 1 to 2 per 1000 per year,[1,7–10] with an exponential increase with age from 1 per 10 000 in young adults to 1 per 100 in the elderly.[6] Data from 2 large US cohorts[11] place the estimated absolute lifetime risk of VTE after 45 years of age at 8.1% (95% CI, 7.1–8.7) overall, 11.5% in blacks, 10.9% in obese individuals, 17.1% among those with the factor V Leiden mutation, and 18.2% among blacks with sickle cell trait. Despite the importance of this disease, there are few contemporary investigations of the total number of VTE events (incident and recurrent) occurring in the United States annually because national surveillance is not performed. The data are thus imprecise, with most prior epidemiological studies limited by small sample size, geographic constraints, or reliance on administrative databases with variable data quality for case ascertainment.

Hospital-acquired VTE, the focus of this report, is commonly defined as VTE occurring during or within 3 months after hospitalization and accounts for >50% of

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the population burden of VTE in the United States.[12–16] Abundant evidence from multiple randomized clinical trials conducted over the past 3 decades conclusively demonstrates that appropriate use of primary thromboprophylaxis in high-risk hospitalized medical and surgical patients is safe, clinically effective, and cost-effective for reducing VTE.[17–22] However, despite these data and the publication of numerous evidence-based consensus guidelines,[23–33] thromboprophylaxis remains either underused or misapplied,[34–47] and population-based studies have shown no temporal declines in either VTE incidence[1,4,48] or case fatality.[49–54] Compounding these issues, public and provider awareness of VTE is low and lags behind that of other common diseases.[55]

Given that much of the morbidity and mortality from VTE are preventable, increased VTE awareness and prioritization of proven, evidence-based primary prevention strategies accompanied by uniform tracking of hospital-acquired VTE should be a national health priority. Indeed, a recent Agency for Healthcare Research and Quality–sponsored study group included interventions to improve prophylaxis rates for VTE as a safety strategy that are ready for adoption now.[56] The purpose of this report is to review the currently understood VTE risk factors, evidence-based guidelines for hospital-based VTE risk assessment and prophylaxis, and current quality measures for VTE prevention. We then propose several policy recommendations that regulatory officials, government, and payers can adopt to reduce the occurrence and impact of this disease.

The call to action is to reduce hospital-acquired VTE by 20% by the year 2030. This call to action grew organically from a summit held at the 2017 American Heart Association (AHA) Arteriosclerosis, Thrombosis and Vascular Biology/Peripheral Vascular Disease Scientific Sessions, during which multiple experts in peripheral vascular disease gathered to discuss population health priorities in peripheral vascular disease. The venous group discussed multiple issues and topics related to VTE and, from the whole group input, came up with what is felt to be a realistic and achievable goal.

COST AND DIAGNOSIS OF VTE

Costs associated with VTE treatment can be used to assess the potential economic benefit of prevention efforts. As recently reported, treatment for acute VTE is estimated to incur direct medical costs of $12 000 to $15 000 (2014 US dollars) per individual in first-year survivors. Approximately 18% of patients with VTE are readmitted within 30 days at a cost of nearly $10 000 per patient,[57] and between 10% and 30% of acute VTE survivors develop recurrent VTE within 5 years, with a peak after discontinuation of anticoagulation.[58] Patients developing VTE often have multiple comorbidities that individually contribute to healthcare use. However, as recently demonstrated, the incremental costs of hospital-related VTE are significant beyond those attributable to coexistent health conditions.[59] Cost estimates commonly exclude subsequent VTE-related morbidity. These include postthrombotic syndrome, occurring in 30% to 50% of patients after proximal DVT,[60] and chronic thromboembolic pulmonary hypertension, occurring in 4% within 2 years of PE survival.[61] When these additional events are factored into cost models, the projected annual cost of preventable hospital-acquired VTE is $7 to $10 billion per year.[7]

Accurate diagnosis is essential to gauge the success of prevention efforts. The diagnosis of VTE is challenging because clinical features are nonspecific and testing can be either falsely positive or falsely negative. Thus, both clinical assessment and objective testing are required. Risk scores for suspected VTE incorporate clinical assessment of pretest probability (PTP) of disease. Although there are several PTP scoring systems, the Wells DVT score, the Wells PE score, and the Geneva PE score are the most widely used and best validated.[62–65] Although PTP assessment alone cannot rule in VTE and generally does not safely rule out VTE, selection of diagnostic tests should align with prior probability (eg, confirmatory testing if high PTP or exclusionary testing if low PTP). Patients with low PTP and a negative quantitative D-dimer can have VTE excluded without the need for imaging. Confirmatory imaging, when required, includes compression ultrasonography, computed tomography angiography, ventilation-perfusion scintigraphy or single-photon emission tomography, magnetic resonance angiography, and echocardiography.

The impact of newer testing modalities is worth mentioning. Data pertaining to this issue derive largely from the Nationwide Inpatient Sample, a weighted sample of US hospital admission data since the 1990s prepared by the Healthcare Cost and Utilization Project. Nationwide Inpatient Sample data consistently show an increasing number of hospitalizations with either a principal or any diagnosis of PE, coinciding with increased availability and use of computed tomography angiography in the late 1990s.[66,67] Stein et al,[54] analyzing Nationwide Inpatient Sample data, found that despite the increasing number of admissions for PE, the percentage of admissions meeting criteria for massive PE has declined, as have hospital length of stay and in-hospital PE mortality, suggesting increasing diagnosis and admission for submassive PE. The clinical significance of subsegmental PE detected by more sensitive chest imaging or of isolated distal DVT detected by whole-leg ultrasound is unknown, and whether treatment benefits outweigh risks is controversial because of the lack of natural history data on the risk of progression, recurrence, chronic sequelae, and bleeding risk in these patients.

Lastly, the issue of surveillance bias related to VTE imaging diagnosis is significant.[68] That is, a lower

threshold for using duplex ultrasonography will detect a significantly greater number of DVTs, but it is unclear whether this correlates with quality of care at a given institution.[69] For example, data from >2500 hospitals with variable VTE prophylaxis and diagnostic imaging rates demonstrate that high-quality hospitals with high prescription of VTE prophylaxis also had higher risk-adjusted VTE rates resulting, in part, from a lower threshold for duplex scanning.[70] Currently, there are no explicit standards or indications for ordering imaging tests to confirm or exclude a VTE outside of clinical judgment. Furthermore, because vigilant care, adherence to hospital screening programs, and more widespread VTE imaging detect asymptomatic disease, health outcomes and costs must be ascertained.

COMMON MEDICAL ILLNESSES ASSOCIATED WITH VTE

Risk factors for acute VTE among hospitalized patients have been extensively investigated and include both inherited and acquired conditions. Major demographic risk factors include older age and obesity.[71,72] Although not an exhaustive list of medical illnesses that are associated with VTE, some prototypical examples follow.

Infection may be a major contributor to VTE. Hospitalization for acute infection has consistently been related to the development of VTE.[72] In a case-control study of >1300 patients with acute VTE in Minnesota, 39.4% of cases were hospitalized with infection compared with 12.7% of control subjects ($P<0.001$).[73] In adjusted analysis, intra-abdominal infection was associated with the greatest risk (odds ratio [OR], 17.8), followed by oral infection (OR, 11.6) and sepsis (OR, 10.7). Symptomatic urinary tract infections and pneumonia were also significant risk factors. Even among those who receive adequate prophylaxis, patients with infections remain at risk for VTE. For example, in a multicenter analysis of 113 patients in the intensive care unit undergoing treatment for severe sepsis, the incidence of acute VTE was 37.2% despite the fact that all patients received thromboprophylaxis, although these patients were all screened for VTE.[74]

Acute stroke is another recognized risk factor for VTE. In an analysis of >30 000 patients in Norway, ischemic stroke was associated with a 3-fold greater risk of VTE compared with no stroke.[75] The highest risk occurred within the first month of the event (hazard ratio, 19.7). These events have important prognostic implications; up to 25% of early deaths after stroke are caused by acute PE.[76] Patients admitted with congestive heart failure are also particularly susceptible to acute VTE[77] because of the condition itself and shared comorbid conditions associated with VTE.[78,79] Furthermore, the risk of VTE has been associated with increasing disease severity, as determined by either left ventricular ejection fraction or NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels.[80,81]

Although not unique to patients hospitalized with the condition, inflammatory bowel disease (IBD) is a significant risk factor for VTE, reflecting an association between inflammation and thrombosis.[82] In multiple large studies, IBD has been shown to increase the risk of VTE by 1.5- to 3.5-fold[83] and correlates with disease activity. Unlike the general at-risk population, patients with IBD often experience thromboembolic events at a younger age,[82] and VTE mortality in patients with IBD is high, with diagnosed IBD conferring an independent 2.5-fold greater mortality.[84] Abnormalities in inflammation and coagulation also may contribute to acute VTE in patients with autoimmune and rheumatological disorders.[85,86] Among all autoimmune diseases, there is a 3-fold increased risk of acute VTE, which is greater among those with active systemic disease.[87] In particular, the odds of developing acute VTE are highest among those with systemic lupus erythematosus (OR, 15.2) and systemic sclerosis (OR, 7.4).[87] Recurrence rates are elevated in such patients, with a 5-year recurrence risk of up to 40%.[86]

MALIGNANCY AND VTE RISK

Cancer accounts for one-fifth of all cases of incident VTE. Across all patients with cancer, the risk for VTE is elevated up to 7-fold over patients without cancer; in certain subgroups such as those with pancreatic cancer or primary brain tumors, the risk for VTE may be increased up to 28-fold.[88] Hospitalization is a major risk factor for VTE in patients with cancer. In a recent large US analysis of nearly 6 million hospitalizations for cancer, VTE was observed in 8.4%.[89] In-hospital mortality occurred in 5.5% of patients with cancer without a VTE diagnosis, in 15.0% of those with any VTE, and in 19.4% of those with PE. Furthermore, analyses of temporal data show that the rate of VTE in hospitalized patients with cancer has nearly doubled in recent years, from 3.5% in 1995 to 6.5% in 2012. The risk of VTE was highest in patients with gastrointestinal, ovarian, lung, and esophageal cancers. Comorbid conditions were contributing factors, with VTE rates increasing progressively from 2.3% in those with no comorbidities to >11% in those with ≥3 major comorbidities. Chemotherapy is a known risk factor for outpatient VTE, but it is unclear whether brief elective admission for chemotherapy truly increases risk. A risk tool has been validated in the hospitalized cancer population in 2 recent cohort studies and incorporates variables such as the site of cancer, elevated leukocyte and platelet counts, low hemoglobin, and high body mass index.[90,91]

Despite the known high risk of VTE in hospitalized patients with cancer and increased mortality risk, patients with cancer are less likely to receive prophylaxis. In an analysis of 2.5 million hospital discharges, hospitalized patients with cancer had the lowest rates of prophylaxis compared with patients with other conditions such as myocardial infarction or severe lung disease.[92] Even when VTE prophylaxis was administered to hospitalized patients with cancer, it was frequently not targeted to those at highest risk.[93] This practice may reflect insufficient clinical trial evidence in this patient population. Specifically, although there are emerging data evaluating the benefit of direct oral anticoagulant use in thromboprophylaxis in outpatients with cancer,[94,95] no cancer-specific randomized trials have evaluated the benefit and risk of inpatient thromboprophylaxis in this population.

COMMON SURGICAL PROCEDURES ASSOCIATED WITH VTE

Overall rates of provoked VTE resulting from surgical procedures account for 20% of all VTE.[7] In addition to procedure type and duration, patient factors such as age and comorbidities, malignancy, prior VTE, and infectious complications all play a major role in postsurgical VTE risk. Older estimates of symptomatic VTE within 90 days after surgery are 0.7% to 0.9% of 1.65 million cases.[96] Contemporary data, based on the American College of Surgeons National Surgical Quality Improvement Program, estimate the rates of VTE to be between 0.5% and 1.6%.[97–100] A higher VTE incidence of 2% to 3% is observed after neurological, orthopedic, oncological, trauma, and emergency surgery.[96,101] Interruptions or delays in prescription of VTE pharmacoprophylaxis in surgical patients have been shown to be associated with a 2- to 3-fold increased risk of VTE,[102] and 35% to 56% of VTE events occur after discharge.[96,103,104]

Surgical risk per se, namely risk attributed to the procedure itself distinct from other factors, is difficult to ascertain because of several factors. First, most patients are now treated with some form of VTE prophylaxis, and it is unethical to withhold prophylaxis from at-risk patients. Second, the type, dosing, and compliance with VTE prophylaxis are less often available from the considerable number of observational studies providing VTE rates compared with fewer controlled clinical trials, thus obscuring the true incidence. Third, postoperative patients are not uniformly and prospectively imaged for DVT, and the trigger for testing is variable from physician to physician.

Comparative differences in VTE rates between nonhospitalized and hospitalized surgical patients are also somewhat difficult to assess on a population basis, in part because of significant differences in patient factors that heighten risk independently of hospitalization.[12,71] Similarly, VTE rates vary between hospitalized surgical and medically ill patients, but these differences attributable to surgery become obscured because many surgical patients have comorbid medical illnesses that contribute to VTE risk. One series comparing VTE risks in medical and surgical patients showed that surgical patients were more likely to have a central venous access but less likely to be receiving active chemotherapy.[105] However, these issues are probably clinically relevant only when a VTE risk assessment tool is chosen, as discussed in the next sections.

LACK OF PATIENT AWARENESS OF VTE AND RISKS

Patient awareness of the risk of VTE associated with hospitalization is low. In a large global survey conducted in 2014, the proportions of respondents who were aware of thrombosis, DVT, and PE (68%, 44%, and 54%, respectively) were lower than the proportions who were aware of other thrombotic disorders such as heart attack and stroke (88% and 85%, respectively) and of nonthrombotic conditions such as hypertension and AIDS (90% and 87%, respectively).[55] Fewer than half of respondents were aware that blood clots were preventable, and awareness that conditions such as cancer, hospitalization, and surgery were associated with risk was quite low (16%, 25%, and 36%, respectively). A similar low awareness was reported in national surveys conducted in individual countries.[106–108] This lack of awareness is not the result of a lack of interest on the part of patients or their families. A survey of patients and families contacted via membership of stakeholder organizations found that participants wanted to learn about VTE symptoms, risk factors, prevention, and complications,[109] preferring to receive education in the context of a doctor-patient encounter. Global initiatives to improve awareness of VTE risk such as World Thrombosis Day[110] reach a large and diverse audience, yet sustainable achievements in symptom recognition, health behaviors, and public perception for patient support and education will require powerful partnerships across public health, clinical practice, and private sectors.

EVIDENCE BASIS FOR VTE RISK ASSESSMENT AND PROPHYLAXIS

Multiple scientific bodies have made recommendations for VTE prevention. The most widely cited guideline is from the American College of Chest Physicians (ACCP), which gives guidance for medical and surgical patients[111] and was published in 2012. The Antithrombotic Therapy for VTE Disease section was updated in

Table 1. Summary of 2012 ACCP Guideline Key Recommendations

For patients at low risk for VTE, prophylaxis is not recommended.
For patients at high or moderate risk for VTE, pharmacological or mechanical prophylaxis is recommended over no prophylaxis.
For patients at high risk for bleeding, pharmacological prophylaxis is not recommended. Instead, such patients should receive mechanical prophylaxis, which can be replaced with pharmacological prophylaxis if the risk of VTE persists and the risk of bleeding decreases.
Duration of guideline recommended prophylaxis:
Medical patients should receive pharmacological prophylaxis for 6–21 d or until discharge from hospital, whichever comes first.
Medical patients should not receive extended prophylaxis beyond the period of patient immobilization or short-term hospital stay.
Surgical patients undergoing major surgery should receive pharmacological prophylaxis for 10–14 d.
The highest-risk surgical patients such as those undergoing abdominal or pelvic surgery for cancer should receive extended prophylaxis (4 wk).
Patients undergoing major orthopedic surgery should receive thromboprophylaxis for a minimum of 10–14 d.
Extended prophylaxis (up to 35 d) is suggested for those undergoing major orthopedic surgery.

ACCP indicates American College of Chest Physicians; and VTE, venous thromboembolism.

2016,[112] although no changes in assessment of risk or prophylaxis were made. Other documents have been issued by the American College of Physicians, American Society of Clinical Oncology, American Society of Hematology, American Academy of Orthopaedic Surgeons, Society of Gynecologic Surgeons, Eastern Association for the Surgery of Trauma, Trauma Quality Improvement Program, and others.[24,33,113–117]

The 2012 ACCP clinical practice guidelines for the prevention of VTE moved clinical practice away from the traditional formula of universal thromboprophylaxis for all hospitalized patients (Table 1). Instead, this edition explicitly advocated prevention strategies that are driven by patients' VTE risk scores, namely the adoption of risk stratification to guide clinicians' decisions to prescribe thromboprophylaxis. For example, in the guideline recommendations for VTE prevention in nonorthopedic surgical patients, patient-oriented VTE risk calculators such as the Caprini and Rogers scores were adopted (see Risk Assessment Tools).[26] For VTE prevention in nonsurgical patients, risk stratification with the Padua Prediction Score risk assessment model was advocated.[28] Since that time, additional risk stratification models for hospitalized medical patients have become available, including the IMPROVE score (International Medical Prevention Registry on Venous Thromboembolism).[118]

Individualized VTE risk stratification allows providers to identify patients who have a favorable risk/benefit ratio for pharmacological prophylaxis but also those patients whose risk/benefit relationship is unfavorable or unknown. These findings, as a whole, challenge the concept that all patients require pharmacological prophylaxis and support a more individualized approach to VTE prophylaxis strategy. Thus, currently recommended prophylaxis strategies become more aggressive as risk level increases, with recommended interventions ranging from no prophylaxis required to mechanical prophylaxis, pharmacological prophylaxis, and then combined mechanical-pharmacological prophylaxis. However, no specific numerical values derived from VTE risk assessments have specific levels of prophylaxis regimens that have been tested in a randomized fashion. Extended-duration prophylaxis (28–35 days) is recommended for the highest-risk surgical patients, although these recommendations are based on older studies that screened asymptomatic patients.

Although the 2012 ACCP guidelines do not recommend performing screening duplex ultrasound in patients without symptoms, other groups suggest that certain populations such as trauma patients may benefit.[119] Another group studied and at high VTE risk includes adult patients in the intensive care unit, in whom standardized surveillance was associated with 52% decreased PE.[120] More data in selected high-risk groups are needed to determine evidence for or against standard screening.

For outpatients, including ambulatory patients and those recently discharged from the hospital, the 2012 ACCP guidelines recommend pharmacological prophylaxis only for patients with solid tumors with additional VTE risk factors who are also at low risk for bleeding. However, the American Society of Clinical Oncology does not specifically recommend discharge VTE prophylaxis.[121] Since the 2012 ACCP guidelines were published, 1 updated systematic review and meta-analysis in acutely ill medical patients (16 studies, 34369 patients) has confirmed that unfractionated heparin significantly reduced the odds of DVT (OR, 0.38 [95% CI, 0.29–0.51]; $P<0.00001$) and PE (OR, 0.65 [95% CI, 0.41–1.00]; $P=0.05$) at a cost of increased major hemorrhage (OR, 1.81 [95% CI, 1.10–2.98]; $P=0.02$). In addition, low-molecular-weight heparin (LMWH) compared with unfractionated heparin significantly reduced the risk for DVT (OR, 0.77 [95% CI, 0.62–0.96]; $P=0.02$) and major bleeding (OR, 0.43 [95% CI, 0.22–0.83]; $P=0.01$).[122]

National Institute for Health and Care Excellence Guidelines 2018

In line with the ACCP clinical practice guidelines, the National Institute for Health and Care Excellence 2018 guidelines on preventing VTE in hospitalized patients include recommendations to manage patients in the hospital and 30 days after discharge from the hospital.[32] Like the ACCP 2012 guidelines, the National Institute for Health and Care Excellence 2018 guidelines also recommend risk assessment to stratify patients' risk of VTE and bleeding and describe interventions to

reduce the incidence of VTE in the hospital and within 90 days after a hospital admission.

American Society of Hematology Guidelines 2018

The American Society of Hematology, in collaboration with the McMaster GRADE Centre, has recently published guidelines on the prevention, diagnosis, and treatment of VTE, including the prevention of VTE in medically ill patients. Nineteen major recommendations for medically ill patients are provided, including pharmacological prophylaxis for all ill patients, no use in patients in nursing homes, not extending prophylaxis beyond the hospital stay, and aspirin in high-risk patients who cannot receive LMWH or sequential compression devices.[33]

RISK ASSESSMENT TOOLS AND MODELS

Several risk scores are used for VTE risk assessment in hospitalized patients. The 2005 Caprini DVT Risk Score (Caprini score) incorporates 40 individual VTE risk factors into a weighted risk model to create an aggregate risk assessment score (Figure 1). This score has been validated to predict a 15- to 20-fold variation in VTE risk among patients undergoing plastic and reconstructive surgery,[124] patients undergoing otolaryngology head and neck surgery,[125] patients receiving gynecology oncology treatment,[126,127] surgical patients in the intensive care unit,[128] and patients undergoing general/vascular/urology surgery.[129]

In addition to identifying baseline risk for VTE, the 2005 Caprini score identifies surgical patients who will or will not benefit from pharmacological prophylaxis. A recent systematic review and meta-analysis specific to the surgical population pooled data from 13 articles (n=14 776) and showed that only patients with 2005 Caprini scores of 7 to 8 (OR, 0.60 [95% CI, 0.37–0.97]; *P*=0.04) and >8 (OR, 0.41 [95% CI, 0.26–0.65]; *P*<0.001) had significant reduction in rates of perioperative VTE when provided with pharmacological prophylaxis. Patients with Caprini scores ≤6, who made up 75% of the surgical patient population as a whole, had

Choose All That Apply:

Each Risk Factor Represents 1 Point
☐ Age 41–60 years
☐ Minor surgery planned
☐ History of prior major surgery (<1 month)
☐ Varicose veins
☐ History of inflammatory bowel disease
☐ Swollen legs (current)
☐ Obesity (BMI >25 kg/m^2)
☐ Acute myocardial infarction
☐ Congestive heart failure (<1 month)
☐ Sepsis (<1 month)
☐ Serious lung disease including pneumonia (<1 month)
☐ Abnormal pulmonary function (COPD)
☐ Medical patient currently at bedrest
☐ Other risk factors: _____

For Women Only (Each Represents 1 Point)
☐ Oral contraceptives or hormone replacement therapy
☐ Pregnancy or postpartum (<1 month)
☐ History of unexplained stillborn infant, recurrent spontaneous abortion (>3), premature birth with toxemia, or growth-restricted infant

Each Risk Factor Represents 2 Points
☐ Age 60–74 years
☐ Arthroscopic surgery
☐ Malignancy (present or previous)
☐ Major surgery (>45 minutes)
☐ Laparoscopic surgery (>45 minutes)
☐ Patient confined to bed (>72 hours)
☐ Immobilizing plaster cast (<1 month)
☐ Central venous access

Each Risk Factor Represents 3 Points
☐ Age >75 years
☐ History of DVT/PE
☐ **Family history of thrombosis***
☐ Positive factor V Leiden
☐ Positive prothrombin 20210A
☐ Elevated serum homocysteine
☐ Positive lupus anticoagulant
☐ Elevated anti-cardiolipin antibodies
☐ Heparin-induced thrombocytopenia
☐ Other congenital or acquired thrombophilia If yes: Type: _____

***Most frequently missed risk factor**

Each Risk Factor Represents 5 Points
☐ Elective major lower extremity arthroplasty
☐ Hip, pelvis, or leg fracture (<1 month)
☐ Stroke (<1 month)
☐ Multiple trauma (<1 month)
☐ Acute spinal cord injury (paralysis) (<1 month)

Total Risk Factor Score _____

Figure 1. Caprini risk assessment tool for surgical patients.
BMI indicates body mass index; COPD, chronic obstructive pulmonary disease; DVT, deep venous thrombosis; and PE, pulmonary embolism. Adapted from Venous Resource Center website[123] with permission. Copyright © 2020, Venous Resource Center, Dr Joseph A. Caprini.

no demonstrable benefit from pharmacological prophylaxis (Caprini score 5–6: OR, 0.96 [95% CI, 0.60–1.53], *P*=0.85; Caprini score 3–4: OR, 1.31 [95% CI, 0.51–3.3], *P*=0.57; Caprini score 0–2: OR, 0.45 [95% CI, 0.10–2.09], *P*=0.31). This same study showed that provision of pharmacological prophylaxis to all patients was associated with a significantly increased risk for bleeding (OR, 1.69 [95% CI, 1.16–2.45]; *P*=0.006). These findings further support consideration of patient-specific VTE risk in the pharmacological prophylaxis decision spectrum.[130]

The Padua Prediction Score (Padua score) (Table 2) identifies an ≈30-fold variation in VTE risk among acutely ill medical inpatients who receive no pharmacological prophylaxis. Patient cohorts whose risk varies between 0.3% and 11.8% can be identified with the Padua score.[131] Several meta-analyses specific to the medically ill inpatient population have demonstrated the benefit of pharmacological prophylaxis in high-risk patients. Existing meta-analyses that showed a benefit for pharmacological prophylaxis were performed in medical inpatients with high-risk characteristics but not explicitly in patients characterized as high risk with the Padua score.[122,133–135] Of note, the initial Padua Prediction Score article showed a statistically significant 90-day VTE risk reduction between patients with a Padua score ≥4 who did and did not receive pharmacological prophylaxis (2.2% versus 11.0%; hazard ratio, 0.13 [95% CI, 0.04–0.40]; *P*<0.001).[131] The 2012 ACCP guidelines for VTE prevention in nonsurgical patients[28] advocated for pharmacological prophylaxis for 6 to 21 days, until full restoration of mobility, or until discharge from the hospital in patients characterized as high risk with the Padua score. Those guidelines explicitly advocated against pharmacological prophylaxis for low-risk patients.

The ability of the 2005 Caprini score to predict 90-day VTE risk and response to prophylaxis has been examined in a large cohort (n=63 548) of medically ill patients. Although there was a linear increase in VTE risk with increasing Caprini score, there was no clear benefit of pharmacological prophylaxis at any Caprini risk level, including those at the highest risk level (Caprini score >8).[136] As discussed, these findings are substantially different from findings in surgery patients. These differences may be the result of the notably different baseline VTE risk between highest-risk (Caprini score >8) medical (1.8%, 124 of 7020)[136] and surgical (8.5%, 143 of 1677) patients.[130] Even among patients with cancer, who are generally acknowledged to be at higher risk for inpatient VTE, there is considerable variation in risk. There are no prospective studies of risk stratification in hospitalized patients with cancer, although 2 recent retrospective cohort studies in the United States and Canada have identified a Khorana Risk Score (Khorana score) cutoff of ≥2 for potential benefit from thromboprophylaxis.[90,91]

Table 2. Padua Risk Assessment Model for Medical Patients

Risk Factors for VTE in Hospitalized Medical Patients	Points
Active cancer	3
Previous VTE (with the exclusion of superficial vein thrombosis)	3
Reduced mobility	3
Already known thrombophilic condition	3
Recent (≤1 mo) trauma or surgery	2
Elderly age (≥70 y)	1
Heart or respiratory failure	1
Acute myocardial infarction or ischemic stroke	1
Acute infection or rheumatological disorder	1
Obesity (BMI ≥30 kg/m^2)	1
Ongoing hormonal treatment	1

BMI indicates body mass index; and VTE, venous thromboembolism.
Adapted from Barbar et al[131] with permission. Copyright © 2010, International Society of Thrombosis and Haemostasis. See also the MDCalc website.[132]

Existing guidelines acknowledge the extreme variation in VTE risk among the overall medical inpatient (0.3%–11.8%, characterized by the Padua score)[131] and surgical inpatient (0.7%–10.7%, characterized by the 2005 Caprini score) populations.[130] Other risk assessment tools include the IMPROVE score, highlighted in recent medical prophylaxis trials (Figure 2).[138,139] Categorizing baseline VTE risk and tailoring the prevention strategy to the patient level represents a paradigm for VTE care individualization. Use of D-dimer to stratify patients in terms of risk deserves further study, and has been used in 1 large trial.[139]

Other Paradigms for Individualization of VTE Risk Reduction

Anticoagulants, when provided as pharmacological prophylaxis against VTE, are typically provided as a fixed dose or "one size fits all," unmonitored strategy in the adult population. However, patients metabolize medications at different rates, and because differential metabolism affects both the risks and benefits of the drug, optimization of the patient's anticoagulant dose represents another paradigm for care individualization. Studies among medical and surgical patients have shown that the majority of patients receive inadequate anticoagulation from a fixed-dose anticoagulation strategy for VTE prophylaxis.[140–143]

Patient-level factors can predict the rapidity of anticoagulant metabolism, making anticoagulant dose adequacy a potential target for VTE risk optimization. Patient weight and extent of surgical injury, in addition to other patient-level factors, correlate with rapidity of enoxaparin metabolism.[141,142,144] Studies have shown that weight-tiered or weight-based

VTE Risk Factors
☐ Previous VTE
☐ Thrombophilia
☐ Lower limb paralysis
☐ Current cancer
☐ Immobilization ≥7 days
☐ ICU/CCU stay
☐ Age >60 years
The incidence of asymptomatic VTE is ≈10 times greater than the incidence of symptomatic disease.

Bleeding Risk Factors	
☐	Gastroduodenal ulcer
☐	Bleeding prior 3 months
☐	Admission platelets <50×109
☐	Hepatic failure
☐	ICU/CCU stay
☐	Cardiovascular catheter
☐	Rheumatic diseases
☐	Current cancer
Sex:	Female
Age:	<40
GFR:	≥60 mL·min^{-1}·m^{-2}

Figure 2. IMPROVE (International Medical Prevention Registry on Venous Thromboembolism) score.
CCU indicates cardiac care unit; GFR, glomerular filtration rate; ICU, intensive care unit; and VTE, venous thromboembolism. Adapted from the Center for Outcomes Research, University of Massachusetts Medical School website[137] with permission. Copyright © 2020, Center for Outcomes Research, University of Massachusetts Medical School.

enoxaparin dosing significantly increases the proportion of patients with adequate anti–factor Xa levels.[144–149] Pharmacist-driven real-time dose adjustment algorithms are also impactful in high-risk patients to optimize anti–factor Xa levels and to decrease symptomatic VTE.[141,142,150] Anticoagulant dose optimization in the setting of VTE prophylaxis is particularly important because at least 3 studies have correlated low anti–factor Xa levels with downstream symptomatic VTE[141] and asymptomatic DVT.[151,152]

Whether the direct oral anticoagulants can improve VTE prophylaxis effectiveness in medical and surgical patients requires further study. However, randomized controlled trials of orthopedic procedural prophylaxis with dabigatran, rivaroxaban, or apixaban compared with LMWH showed at least equal efficacy and less bleeding.[153–155] Similarly, LMWH is more effective than placebo for decreasing VTE, and rivaroxaban is noninferior to LMWH in VTE incidence to 35 days in acutely ill medical patients.[156,157] However, extended VTE prophylaxis benefit in medically ill patients with betrixaban compared with LMWH was not shown,[138] and extended prophylaxis with rivaroxaban was not associated with reduced VTE.[139]

UNDERUSE OF VTE PROPHYLAXIS

Although there are many options for VTE prophylaxis and multiple guidelines supporting their use, these interventions are often underprescribed. A 2008 multinational study of 358 hospitals in 32 countries showed that the use of recommended pharmacological prophylaxis regimens was low.[105] Although 51.8% of hospitalized patients were considered to be at risk for VTE by the risk assessment model promoted in the ACCP 2004 guidelines on VTE prevention,[158] only 50.2% of those at-risk patients had orders for pharmacological prophylaxis. Of those patients who were deemed at too substantial a risk for bleeding to receive anticoagulant prophylaxis, few patients were prescribed mechanical prophylaxis. In contrast, patients who were considered low risk for VTE tended to be "overprophylaxed," with about one-third of both low-risk surgical and medical patients receiving prophylaxis that was not indicated by risk factor assessment.

A retrospective observational study of Canadian hospitals showed that fewer than one-quarter of acutely ill medical patients were prescribed any form of VTE prophylaxis, despite the fact that 90% of them had indications for it.[47] US hospitals performed no better, with only 12.7% of medical patients and 16.4% of surgical patients prescribed appropriate prophylaxis according to accepted guidelines.[159]

Even patients with cancer, who are at particularly high risk for VTE, often are prescribed inadequate prophylaxis. A study of hospital discharge information for >70 000 patients with cancer admitted for ≥6 days, of whom 58% were medical patients, showed that only 53.6% were prescribed prophylaxis. Only 27% were prescribed appropriate VTE prophylaxis as recommended by evidence-based guidelines.[160]

Recent data show increasing rates of prescribed prophylaxis. A consortium of hospitals in Michigan examined 44 775 medical patients admitted to non–intensive care unit floors for >2 days and risk-stratified them according to the Padua Prediction Score. The authors found much high rates of prophylaxis, with 78.0% of patients deemed at high risk for VTE having orders for some form of prophylaxis.[161] The authors also found high rates of inappropriate prophylaxis orders, with 77.9% of low-risk medical patients prescribed excess prophylaxis, defined as the use of pharmacological prophylaxis, mechanical prophylaxis, or both, suggesting the indiscriminate use of prophylaxis.

INTERVENTIONS TO INCREASE VTE RISK ASSESSMENT AND THROMBOPROPHYLAXIS

VTE prevention is a key element in reducing VTE-related mortality and morbidity in hospitalized medical and surgical patients. Data on rates of use of VTE risk assessment models are sparse. However, a recent study suggests that, when used consistently, VTE risk assessment models may reduce rates of prophylaxis without adversely affecting rates of VTE. Researchers compared retrospective data for patients admitted to 1 hospital before the introduction and widespread adoption of VTE risk assessment models (the Padua and IMPROVE VTE risk scores) with prospective data for patients admitted after the introduction of risk assessment models. Results for 413 patients demonstrated no significant difference in rates of PE or major bleeding. Only 43.3% of prospective patients had pharmacological prophylaxis ordered compared with 56.7% in the retrospective group.[162] The authors showed that risk-based assessment led to reduced healthcare expenditures from appropriate pharmacological prophylaxis, with no detriment to patient safety.

In an attempt to improve the adequate prescription of VTE thromboprophylaxis in hospitalized patients, the efficacy and safety of various types of passive and active system-wide interventions have been assessed in different hospital settings all over the world.[163–166] Although passive interventions such as continuing education, dissemination of guidelines, audit, and feedback were found to be insufficient, active mandatory interventions such as alerts (computer or human) appeared to be successful at improving rates of VTE prophylaxis in clinical practice. This conclusion was supported by the most recent updated Cochrane review that improved on prior meta-analyses conducted in this area in that it included a large number of participants (13 randomized controlled trials; n=35 997 participants) and was restricted to studies with randomized designs, yielding less widely differing estimates (ie, heterogeneity) across studies, more precision of the estimates of effect (ie, narrower CIs), and overall higher levels of evidence.[167]

Early studies on computerized alerts predate many modern electronic medical records and could be performed only on systems with integrated databases. Kucher and colleagues[168] reported 2506 medical and surgical patients at high risk for VTE who were receiving no VTE prophylaxis, with the responsible physician randomly alerted or not to the patient's VTE risk level. Alerted providers were also linked to the hospital's VTE prevention guidelines with the option to order prophylaxis. Patients whose providers were alerted were significantly more likely to receive mechanical (10.0% versus 1.5%; *P*<0.001) and pharmacological (23.6% versus 13.0%; *P*<0.001) prophylaxis, and the computer alert reduced 90-day VTE risk by 41% (hazard ratio, 0.59 [95% CI, 0.43–0.81]; *P*=0.001).[168] This important study identified the importance of clinical decision support systems (CDSS).

Johns Hopkins implemented a service-specific and mandatory VTE decision support tool into its online order entry system. A pre/post analysis in 1599 patients undergoing trauma surgery showed that CDSS implementation significantly increased provision of guideline-adherent VTE prophylaxis (66.2% versus 84.4%; *P*<0.001). Perhaps more important, the rate of preventable harm from VTE decreased significantly after CDSS implementation (1.0% versus 0.17%; *P*=0.04).[169] In a separate analysis, the same group identified that, at baseline, there were sex and racial disparities in the provision of appropriate VTE prophylaxis for both the internal medicine and trauma surgery populations. Implementation of a CDSS significantly improved provision of compliant VTE prophylaxis and eliminated disparities in provision.[170] The Johns Hopkins model was subsequently implemented at the University of Virginia as a mandatory CDSS embedded into the online order entry system for patients undergoing general surgery. Implementation of the CDSS was associated with a significant decrease in 30-day VTE (1.25% versus 0.64%; *P*=0.033) and allowed the institution to improve its ranking for VTE from the ninth to first decile among 760 hospitals participating in the National Surgical Quality Improvement Program.[171]

Boston University implemented risk stratification into its online order entry system for inpatient general and vascular surgery patients on the basis of National Surgical Quality Improvement Program data showing that its hospital was a high outlier for VTE. Individualized VTE risk stratification was mandatory, and providers received an automated suggestion about appropriate prophylaxis type and duration based on calculated Caprini score. Compliance with recommended prophylaxis regimens was high for patients at low to moderate VTE risk (100%) and for patients at high risk for VTE (89%). At the institutional level, mandatory risk stratification significantly decreased rates of DVT from 1.9% to 0.3% and PE from 1.1% to 0.5%, again highlighting that there are patient- and hospital-level benefits from CDSS implementation.[172]

Unfortunately, many patients prescribed thromboprophylaxis may not receive it. For instance, a study of >10 000 patient hospital stays showed that 11.9% of prescribed pharmacological prophylaxis doses were not administered.[173] Patients missing >1 dose of prophylaxis accounted for ≈80% of unadministered doses. A prospective trial in trauma patients found that interrupted VTE prophylaxis was associated with 5-fold increased DVT incidence.[174] Another study examining this issue found that patient refusal accounted for 39% of missed LMWH doses and 44% of missed unfractionated

heparin doses,[175] suggesting that improved patient education efforts could potentially improve patient acceptance and rates of administered prophylaxis. However, subcutaneous anticoagulant doses are more often missed than other scheduled medications[176] such as orally administered medications.[177] Thus, whether oral agents may be associated with improved VTE prophylaxis compliance bears further study. Improving patient engagement by directed education for VTE prophylaxis compliance has been proven effective.[178,179]

The use of payment incentives to reward increased quality of health care, so-called pay for performance, has been advocated as a means of encouraging more widespread ordering of thromboprophylaxis. For example, a hospital group created provider-level dashboards that showed individual physicians' prophylaxis orders over a period of 6 months, followed by a pay-for-performance program that gave graduated payments for the highest rates of prophylaxis orders. Researchers found that providers' rates of ordering prophylaxis increased from a baseline of 86% to as high as 94% with a combination of the dashboard and pay-for-performance measures.[180] A project aimed specifically at residents using pay for performance achieved even higher results, with increases in VTE prophylaxis from 89.7% to 100% over 12 months.[181]

In summary, alert interventions (computer or human) and multifaceted interventions included in clinicians' workflow were the most effective system-wide interventions that helped healthcare providers improve the use of appropriate VTE prophylaxis and thereby reduce the morbidity and mortality of VTE in hospitalized patients. The adoption of specific hospital system-wide measures is therefore a key element in improving the prevention of VTE in hospitalized patients.

TRACKING OF NATIONAL VTE OUTCOMES

Accurate national documentation of VTE risk stratification, risk-appropriate application of VTE prophylaxis, and quantification of rates of VTE outcomes is possible but is currently challenging for several reasons. Although many hospitals use a procedural or quality improvement registry to improve care (and to be compliant with merit-based incentive payment system), this is neither uniform across the United States nor mandated by payers or quality improvement bodies.

National VTE measures have been developed to address the gaps in VTE thromboprophylaxis and include initiatives from the Agency for Healthcare Research and Quality, Centers for Disease Control and Prevention, and The Joint Commission.[182] The Agency for Healthcare Research and Quality developed its set of patient safety indicators to screen for hospital-associated adverse events in the early 2000s.[183] Patient safety indicator 12, postoperative VTE, is considered a preventable hospital-acquired condition. Similarly, The Joint Commission and the National Quality Forum joined together to develop standards for the prevention of VTE and care of patients with VTE. The groups created 6 VTE core measures aligned with Centers for Medicare & Medicaid Services, which were endorsed by the National Quality Forum in 2008. The 3 measures still in use are VTE-1, which examines whether patients admitted to the hospital are prescribed thromboprophylaxis; VTE-2, which looks specifically at patients in the intensive care unit; and VTE-6, which reports the rate of hospital-acquired VTE.[184] The Centers for Medicare & Medicaid Services also require hospitals to report Surgical Care Improvement Project measures related to VTE, specifically the number of patients for whom prophylaxis is ordered at surgery and the number of patients who receive at least 1 dose of prophylaxis within 24 hours before or after surgery. The current Centers for Medicare & Medicaid Services ruling to have VTE be a never event in total knee or hip arthroplasty[185] has been criticized because it does not reflect quality of care.[186] For example, a recent report highlights that more than half of symptomatic VTE occurred despite optimal audited pharmacological prophylaxis.[187,188] It is unclear whether these penalties will continue or will be broadened to include other illnesses or surgical procedures.

The penetrance of uniform definitions of VTE and objective determination of VTE occurrence is unclear. For example, National Quality Forum measure No. 23 tracks prescription of VTE prophylaxis administration, whereas the Agency for Healthcare Research and Quality patient safety indicators include only overall VTE outcomes.[189] A prototypical surgical quality registry is the American College of Surgeons National Surgical Quality Improvement Program.[98,100,104] This has objective VTE definitions and tracks VTE occurrence to 30 days via trained nurse abstractors. It is limited because this registry does not track prescription of prophylaxis, is voluntary, and involves a modest cost; in addition, data on patients who may have a VTE after 30 days are not captured.[188] Furthermore, the National Surgical Quality Improvement Program does not provide variables to allow a Caprini score to be generated. Ideally, tracking VTE rates to 90 days after intervention or after hospitalization is ideal because the risk of VTE remains elevated through that time frame.[8,10,96]

The use of *International Classification of Diseases, 10th Revision*, codes compared with ninth revision codes might allow increased granularity and tracking of VTE rates going forward. For example, *International Classification of Diseases, Ninth Revision, Clinical Modification*, includes ≈10 codes for VTE. The 10th edition codes for VTE exceed 30, with specific capture of location and laterality of DVT, information that was not

included with *International Classification of Diseases, Ninth Revision, Clinical Modification*. This may provide a new benchmark and a way to more specifically track incident VTE rates at each hospital. However, the limits and pitfalls of administrative data such as coding errors, preexisting conditions, and lack of objective clinical definitions remain.

Another potential for improving risk assessment and prophylaxis prescription is statewide and regional quality collaboratives. For example, in the state of Michigan, quality improvement registries exist that include almost all major hospitals, including a hospital medicine registry and several surgical registries. Published studies from these registries have highlighted VTE rates, risk stratification, and prospectively defined prophylaxis use, as well as prescription of VTE prophylaxis of >75%.[136,190,191] However, registries are costly to run, and hospital participation is voluntary.

Lastly, these measures and potential new approaches still need to address VTE that occurs despite adequate prophylaxis, to assess whether prescribed VTE prophylaxis was actually administered, and to account for whether patients received continuous prophylaxis during their hospital stays.[189] A recent statewide quality effort documented that ≈18% of patients failed to receive pharmacoprophylaxis, primarily because medications were not ordered or because of patient refusal.[192] This study underscored a tracking system for issues with prophylaxis that is more comprehensive than many current measures. Indeed, nursing interventions, patient education, and pharmacist-led initiatives aimed at reducing missed doses and addressing patient refusal also may help.[193,194]

PROPOSED POLICY STEPS TO DECREASE VTE IN HOSPITALIZED PATIENTS BY 20% BY 2030

The International Society on Thrombosis and Haemostasis has recently put forward a call for risk assessment in all hospitalized patients, similar to our document and as highlighted by World Thrombosis Day.[195] Much like this document, the emphasis is on the process measure of VTE risk assessment rather than an institution's VTE rate as a marker of quality and affecting care. We further support national tracking of VTE incidence to assess time trends as diagnostic testing, screening, and treatment algorithms evolve and enduring programs for public awareness to improve symptom recognition, medication adherence, and patient/family support and education.

Lau et al[189] nicely summarized the ideal state for VTE prevention: standardized assessment of risk, provision of risk-appropriate VTE prophylaxis, prevention of missed chemoprophylaxis doses, and definition and tracking of rates of preventable VTE. Preventable VTE is defined as occurring in a high-risk patient not prescribed adequate VTE prophylaxis, whereas nonpreventable VTE occurs in those who have received appropriate risk assessment and thromboprophylaxis with documentation of compliance. Objectively determined VTE is defined as a clinically manifest VTE, confirmed with standard imaging. Many areas, however, require further study and further research to provide evidence for practice and policy (Table 3).

Table 3. Areas of Further Research to Inform Policy Development and Clinical Guidance

Determine what should constitute preventable VTE across medical and surgical patients.
Compare chart-abstracted VTE rates with *ICD-10* code rates in all US hospitals to assess precision and completeness.
Evaluate EMRs as a system to automatically provide risk assessment and suggest an appropriate level of VTE prophylaxis.
Define the effect of surveillance bias on VTE rates; consider a study of indications and triggers for VTE diagnostic studies and potential standardization of these across clinicians and hospitals/institutions.
Evaluate the best methods to disseminate VTE risk assessment and prophylaxis education to practitioners and VTE risks to patients and families.
Compare the VTE risk scoring prospectively against specific pharmacological and mechanical prophylaxis.
Evaluate and test best methods to prevent missed prophylaxis dosing and to improve compliance.

EMR indicates electronic medical record; *ICD-10*, *International Classification of Diseases, 10th Revision*; and VTE, venous thromboembolism.

Given the current state of nonuniform individualized risk assessment and the overuse and underuse of VTE prophylaxis in low- and high-risk patients, respectively, we believe the evidence and tools are now available to allow several VTE prevention goals to be accomplished, in part through the government and payer policies listed below.

- The AHA supports performing VTE risk assessment and reporting the level of VTE risk in all hospitalized patients.
- The AHA supports the use of the indicator preventable VTE as a benchmark for hospital comparison and pay-for-performance programs (eg, Medicaid, Medicare).
- The AHA supports appropriations for collaborative initiatives across public health, clinical practice, and private sectors to improve public awareness of VTE.
- The AHA supports national tracking of objectively determined VTE with the use of standardized definitions of VTE that occurs within 90 days of a hospital stay.
- The AHA recommends a central steward for data tracking VTE risk assessment, application of VTE prophylaxis, and VTE rates for all hospitals such as the Core Quality Measures Collaborative.[196]

ARTICLE INFORMATION

The American Heart Association makes 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.

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Writing Group Disclosures

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Peter K. Henke	University of Michigan	None	None	None	None	None	None	None
Mark A. Creager	Dartmouth Hitchcock Medical Center	None	None	None	None	None	None	None
Natalie S. Evans	Cleveland Clinic	None	None	None	None	None	None	None
Susan R. Kahn	McGill University	CIHR and multiple nonprofit and for-profit funding partners†; Tier 1 Canada Research Chair in Venous Thromboembolism†; investigator of the CanVECTOR Network (funded by Canadian Institutes of Health Research CDT-142654)*	None	None	None	None	Advisory Board for Pfizer*; Sanofi*; Servier*	None
Alok A. Khorana	Cleveland Clinic	Array*; BMS*; Leap*; Merck*; research support from the Sondra and Stephen Hardis Chair in Oncology Research†; National Heart, Lung, and Blood Institute (U01HL143402, R34 HL127156)†	None	None	None	None	Bayer†; Halozyme*; Janssen†; Pfizer*; Pharmacyclics*; Pharmacyte*; Sanofi†; Seattle Genetics*; Trisalus*	None
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Aruna D. Pradhan	Brigham and Women's Hospital	None	None	None	None	None	None	None
Eric A. Secemsky	Beth Israel Hospital	None	None	None	None	None	None	None

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*Modest.

†Significant.

Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
Elliott R. Haut	Johns Hopkins University	Agency for Healthcare Research and Quality (PI of R01 research grant)†; National Heart, Lung, and Blood Institute (Co-I of R21 research grant)†	Patient-Centered Outcomes Research Institute (PI and Co-I of numerous PCORI-funded projects)†	None	None	None	None	None
Scott Kaatz	Henry Ford Hospital	Janssen (research funds to my institution; I was the site PI)*	None	None	None	None	Janssen†; Pfizer†; Portola*; Roche*	None
Gary Raskob	University of Oklahoma	CDC (VTE surveillance)†	None	None	None	None	Janssen†; Bayer†; Daiichi Sankyo†; Portola†; BMS*; Pfizer*; Tetherex*	None
Jeffrey I. Weitz	Thrombosis & Atherosclerosis Research Institute (Canada)	None	None	None	None	None	None	None

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*Modest.

†Significant.

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