Venous Thromboembolism Prophylaxis in Thoracic Surgery

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Abstract

Venous thromboembolism (VTE) is a dreaded post-operative complication in nearly all surgical specialties. There has been a decades-long effort to identify patients with high risk for post-operative VTE and determine the most appropriate course of action to prevent VTE occurrence. The 9th edition of the American College of Chest Physicians (ACCP) guidelines consider thoracic surgery patients to be at moderate risk for post-operative VTE. Despite recognition of post-operative VTE risk in thoracic surgery patients, there is a lack of consensus regarding the best practices to reduce VTE occurrence. VTE Risk Assessment Models (RAMs), including the Caprini RAM, have been developed outside of thoracic surgery to risk stratify patients for post-operative VTE and recommend appropriate prophylactic measures. Such interventions include early mobilization and inpatient mechanical compression devices, as well as chemoprophylaxis with unfractionated heparin and low-molecular-weight heparin, among other anticoagulants. Implementation of such interventions into general and vascular surgery have produced encouraging results with up to 84% reduction in VTE rates. Modification and application of existing RAMs in the thoracic surgery setting have shown promising preliminary results. Despite improvements achieved by implementing modified RAMs in thoracic surgery services at individual institutions, there are currently no field-specific guidelines to solidify practices nationwide. As a result, there remains considerable variability regarding patient screening, risk stratification, and VTE chemoprophylaxis practices. As most post-operative VTE occur after patient discharge, field-specific guidelines surrounding extended courses of chemoprophylaxis are needed. Large multicenter studies evaluating the implementation of specific VTE RAMs into thoracic surgery services are likely required before a standardized approach to VTE prevention can be achieved.

Introduction

Venous thromboembolisms (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT), result in significant post-operative morbidity and mortality, and presage reduced longevity. Post-operative VTE has been associated with an eight-fold increase in mortality after general lung resection,[1] and mortality due to VTE after lung resection for cancer was reported to be 19.8%.[2] The occurrence of post-operative VTE is difficult to predict and varies considerably amongst thoracic surgery patients. Factors implicated in the inability to precisely ascribe incidence data to VTE in thoracic surgery patients include disease-specific factors, varying methods of prophylaxis used during the perioperative period, and variations in screening practices.[3,4,5]

According to the American College of Chest Physicians (ACCP) 9th edition Evidence Based Clinical Practice Guidelines, most thoracic surgery patients are considered to be at least at moderate risk for development of post-operative VTE when compared to other surgical specialties.[6] Gould et al. reported that among nearly 700 patients who underwent thoracotomies for lung cancer, symptomatic VTE occurred in 1.7% of patients, including PE in 1.3%, despite routine use of pharmacologic prophylaxis.[6] A study published in 2004 by Nagahiro et al. investigating the benefit of mechanical VTE prophylaxis in thoracic surgery patients between 1995 and 2000 reported that 2% (7 of 344) of patients who did not receive prophylactic mechanical intervention developed post-operative VTE.[7] While the number of patients in this study is limited, it does provide some insight into the baseline incidence of symptomatic VTE in thoracic surgery patients in the absence of pharmaceutical prophylactic measures. In a retrospective study of oncologic anatomical lung resections and esophagectomies in an urban safety-net hospital, Hachey and colleagues found a 60-day post-operative VTE rate of 5.2% and 14.3%, respectively.[1, 8] Alternatively, in a 2016 study measuring post-operative VTE in patients undergoing oncologic lung resections at two tertiary centers in Ontario, 12.1% of patients developed VTE, of which 8.9% were PE and 1.9% DVT, despite receiving institutional VTE mechanical and chemoprophylaxis.[9] The markedly high VTE incidence reported in certain studies is a result of screening all post-operative patients for VTE, irrespective of symptomatic presentation. Subsequently, the detection of subclinical VTE has led to reports of VTE incidences ranging from approximately 2-14%.[4, 10] These variable incidence data highlight the inconsistencies and difficulties associated with determining post-operative VTE incidence in thoracic surgery patients.

Risk factors associated with VTE are numerous. Surgical patients have an inherently elevated risk of developing VTE partially explained by systemic inflammation, a hypercoagulable state induced by major surgery, vessel injury, and venous stasis during and following the operation.[11, 12] The risk of developing VTE in thoracic surgery patients varies by procedure. Gould et al. reported that extended pulmonary resection, pneumonectomy, and esophagectomy carry a higher risk of post-operative VTE compared to other thoracic surgical procedures.[6] Forty-two day VTE prevalence as high as 7.4% has been reported for patients receiving pneumonectomy for lung cancer.[13] Independent of the risk associated with specific surgical procedures, numerous congenital and acquired VTE risk factors exist. Selected acquired factors associated with VTE development include advanced age, chemotherapy, comorbidities, history of VTE, immobility, malignancy, obesity, oral

contraceptives, and pregnancy.[11, 12]

A significant number of post-operative VTEs occur post-discharge, with an estimated one-third of cancer surgery-related-VTE occurring after the patient leaves the hospital.[14] In a study assessing VTE after pneumonectomy for malignancy, Mason et al. reported the peak incidence of VTE to be at one week after the operation, which in many circumstances, exceeds the patient's length of stay.[13] In a 2016 study by Hachey et al., the median time from lung resection to VTE diagnosis was 10 days.[1] With recent incentives to return patients home safely and rapidly, and the increased use of minimally invasive procedures, there has been a reduction in overall hospital length of stay. White et al. reported that 0.7% of post-anatomical pneumonectomy and 1.3% of post-open lung biopsy VTEs occurred post-discharge.[3] The risk for developing post-operative VTE has been reported to persist up to 12 weeks, as illustrated in a British study assessing the duration of post-operative VTE risk in nearly one million middle-aged women.[15]

Diagnosis of VTE, irrespective of surgical intervention, results in substantial cost to patients, insurance companies, and providers. Estimates of the economic burden associated with VTE diagnoses in 2007 revealed that mean costs per PE admission and readmission were both approximately $15,000, and mean costs for DVT admission and readmission were approximately $10,000 and $12,000, respectively.[16] In a 2004 study, the estimated cost of thromboembolic surgical complications reached over $18,000.[17] Due to the morbidity, mortality, and cost to both individuals and institutions, prevention of VTE has become a significant area of focus, and is the subject of a call to action by the office of the US surgeon general, in addition to the National Quality Forum, Center for Medicare and Medicaid Services (CMS), and Joint Commission on Accreditation of Health Care Organizations (JCAHO).[12, 18]

Current Guidelines

As VTE events can partially be prevented with pharmacologic and mechanical prophylaxis, several methods have been developed to risk-stratify surgical patients' propensity for VTE.[12] The ultimate goal is to identify high-risk patients and initiate risk-adjusted prophylaxis to reduce their risk of VTE development. There is a lack of consensus amongst providers with regards to selection of risk-stratification methods and appropriate prophylactic measures, including the duration of post-discharge prophylactic anticoagulation, if any. Limited data and lack of comprehensive thoracic surgery-specific VTE prevention guidelines lead to considerable variability in practice. A 2016 study surveying the practices of thoracic surgeons with regard to VTE prophylaxis for esophagectomy patients found that 92% of respondents would follow esophagectomy-specific guidelines, if developed. However, the lack of such guidelines has led to delays in prescribing post-operative prophylaxis, as well as inconsistent, suboptimal dosing, and lack of adequate post-discharge prophylaxis.[19]

The most recent VTE prophylaxis guidelines are from the 9th edition ACCP Evidence Based Clinical Practice Guidelines. The thoracic surgery-specific prophylaxis recommendations provided in the ACCP guidelines are based on two small studies, one investigating varying doses of low-dose unfractionated heparin (LDUH), and the other investigating a fixed-dose and weight-adjusted dose of nadroparin.[6] According to the ACCP guidelines, grade 1B evidence supports the use of routine VTE prophylaxis for thoracic surgery patients throughout the post-operative period with LDUH, or low molecular weight

heparin (LMWH).[6] However, the guidelines cite moderate evidence to suggest that pharmacologic prophylaxis with LDUH or LMWH prevents more VTE than it causes bleeding events.[6] The ACCP reports low quality evidence supporting the use of mechanical prophylaxis (in the form of intermittent compression devices) over no prophylaxis, but does endorse the use of mechanical prophylaxis in cases of increased bleeding risk from pharmacologic prophylaxis.[6]

The ACCP recommendations are stratified based upon tiered VTE risk. Thoracic surgery patients at moderate risk for VTE with low risk of bleeding are recommended to receive LDUH or LMWH, or mechanical prophylaxis. Thoracic surgery patients at high risk for VTE without high risk for bleeding are recommended to receive LDUH or LMWH, *in addition to* mechanical prophylaxis. Thoracic surgery patients at high risk for VTE with a high risk for bleeding are recommended to receive mechanical prophylaxis until bleeding risk can be reduced enough to safely receive pharmacologic prophylaxis.[6]

It is worth noting that despite having recommendations tailored to varying risk of VTE development, the ACCP guidelines do not provide recommendations for the VTE risk stratification of thoracic surgery patients. There is mention of two methods currently used to stratify patient-specific VTE risk, the Caprini Risk Assessment Model (RAM) and the Rogers Score; however, the ACCP makes no recommendation for the use of one stratification system over the other, nor does it suggest or evaluate any alternatives.[6] Furthermore, there is evidence that the ACCP guidelines may be insufficient to reduce VTE risk in thoracic surgery patients. Despite providing patients with LMWH from surgery through discharge, a practice consistent with current ACCP guidelines, a study using computed tomography (CT) to screen for post-lung resection PE reported an incidence of 14%.[10] While no validated baseline is available to compare the effect of ACCP guideline use on VTE prevention, a PE rate of 14% remains elevated by all standards of care. As this study used CT to screen all patients for PE, a practice not routinely employed, the elevated incidence of PE likely included patients that may not have become symptomatic. It is important to note that there is no recommendation in the ACCP guidelines regarding the duration of prophylactic anticoagulation, nor is there mention of the use of post-discharge prophylaxis. While current ACCP guidelines provide an evidence-based framework for the use of pharmaceutical and mechanical postoperative VTE prophylaxis in the field of thoracic surgery, several questions remain unanswered, including the exact duration of VTE prophylaxis, as well as the optimal method for VTE risk stratification. Specifically, the current ACCP guidelines may be insufficient to properly address the preponderance of VTEs occurring post-discharge. Much of the analysis of VTE risk in thoracic surgery was derived from investigations undertaken in other specialties, including general and abdominopelvic surgery.[6] While inter-specialty VTE risks may be applicable to all surgical patients, providing recommendations on best practices in thoracic surgery should ideally be based upon robust field-specific data.

Current Practices

In the absence of comprehensive guidelines, contemporary VTE prevention practices in thoracic surgery vary by clinician and institution. Mechanical prophylaxis, including sequential compression devices, has become common practice in many surgical services, as has the perioperative use of unfractionated heparin.

A significant source of practice variation involves identification of patients in whom the risk of developing VTE outweighs the risks of completing an extended course of chemoprophylaxis. Additionally, variation in practices includes determination of appropriate chemoprophylactic agent and duration of post-discharge prophylaxis. In a 2017 comprehensive review, Jacobs and Pannucci outlined existing RAMs that have been used with varying degrees of success to stratify patients by risk for VTE development. Among the RAMs outlined in the article are the Caprini RAM, the Rogers RAM, Pannucci Inpatient and Outpatient Scores, NAVAL score, as well as other condition-specific RAMs including the Pediatric Trauma Patient, Ventral Hernia Repair, Adult Trauma Patients, and the Risk Assessment Profile for Trauma Patients (RAPT).[12]

The Caprini RAM is currently the most widely utilized of the aforementioned RAMs, validated in various fields such as general, urologic, and vascular surgery, and later in surgical ICU patients, head and neck surgery, plastic and reconstructive, gynecologic, and orthopedic surgery.[12] From its inception in the early 1990's, the Caprini RAM has been revised over many years. Currently, the two major forms of the Caprini RAM are the 2005 and 2010 editions, of which the 2005 Caprini RAM has more external validation, and was found to have better predictive capability compared to the 2010 version in a cross-over study performed in plastic surgery patients.[20] The 2010 version differs from the 2005 version by ascribing higher point values for increasing duration of operation, as well as assigning increasing point values for increasing body mass index. The 2010 version also differentiates between past history of cancer, and current cancer.[12]

The Caprini RAM is utilized in the following manner: a Caprini score is calculated for an individual patient based upon presence or absence of 40 weighted risk factors (Table 1). Patient scores are categorized as lowest (0 points), low (1-2 points), moderate (3-4 points), high (5-8 points), or highest risk (>9 points) for the development of post-operative VTE.[21] Based on the risk group, a pre-determined length of post-discharge prophylactic anticoagulation is prescribed, ranging from none (low through moderate risk groups) to 30 days (highest-risk group). Studies validating the 2005 iteration of the Caprini RAM demonstrate that increased scores show statistically and clinically significant increase in VTE rate.[12] In fields that have validated any version of the Caprini RAM, there is a strong correlation with high Caprini score and risk for VTE.[12] However, due to the lack of field-specific data and guidelines, the Caprini RAM is not yet widely used throughout thoracic surgery, although recent studies have begun to prove its utility.

The Rogers RAM is another risk assessment model that is presented in the ACCP guidelines and has undergone some form of external validation.[6, 12] The Rogers RAM was created using the Veteran's Affairs-Patient Safety in Surgery (VA-PSS) database, and used statistical modeling to identify and grade VTE risk factors.[12] External validation of the Rogers RAM has only been performed in gynecology oncology patients; there is currently no literature exploring the use of Rogers scoring system in thoracic surgery.

There is a general agreement regarding the risk factors associated with post-operative VTE. This agreement is evident in surveys of clinicians' opinions, as well as the fact that many of the same risk factors are present in existing risk stratification and scoring systems. A 2017 survey of practice patterns for VTE prophylaxis amongst Canadian thoracic

surgeons treating thoracic malignancies revealed that there is virtually unanimous agreement upon the risk factors associated with post-operative VTE.[4] Additionally, providing perioperative and pharmacological prophylaxis to surgical patients until discharge was reported to be common practice among survey respondents, with VTE chemoprophylaxis provided until discharge by all participants.[4]

Despite agreement upon who is considered high-risk for VTE, there exists practice variation surrounding interventions to prevent VTE. Among the respondents to the Canadian survey by Agzarian et al., there was limited agreement in the type (pharmacologic, mechanical, or both), as well as the timing of initiation and duration of VTE prophylaxis.[4] This sentiment was mirrored in a survey of thoracic surgeons' opinions on post-operative VTE risk reduction in patients undergoing esophagectomies. Most thoracic surgeons surveyed agreed that esophagectomy patients were at increased VTE risk.[19] However, it was revealed that many of the respondents to the survey used suboptimal peri- and post-operative anticoagulation dosing, and that many providers did not extend anticoagulation into the post-discharge period.[19] These respective surveys reflect the current inconsistencies in VTE prevention opinions and practices currently observed in thoracic surgery. With a large at-risk oncologic population and a growing emphasis on patient safety within the healthcare industry, the thoracic surgery community must recognize the lack of standardization in the common goal of VTE prevention.

Practices in VTE prevention

Several interventions for early detection and prophylaxis of postoperative VTE events have been implemented in a growing number of surgical practices over the past twenty years. Both DVT and PE events were initially thought to be rare complications manifested through significant symptomatic presentations. However, a recent study from the Cleveland Clinic showed that nearly half of inpatient VTE events following pneumonectomy were asymptomatic.[22] Similarly, in a study investigating the prevalence of VTE events following pulmonary oncologic resection by colleagues at McMaster University in Canada, 80% of VTE were found to be asymptomatic at the time of diagnosis.[9] These studies underscore the idea that post-operative VTEs can occur undetected by clinicians and patients alike in the absence of screening programs. And while some proponents of early VTE prevention support targeted and risk-based screening programs, the role, value, and impact of such a broad intervention is yet to be determined.[23]

Surgical institutions across the nation have implemented specific VTE reduction programs with efforts ranging from early mobilization and ambulation efforts, to systematic wearing of pneumatic compression stockings for intra- and postoperative patients, as well as VTE chemoprophylaxis. As previously discussed in this review, current practices in VTE chemoprophylaxis vary widely among practices in initiation timing, duration, agents of choice, and outpatient requirements. With the concurrent lack of field-specific guidelines and the drive to avert postoperative VTE events in surgical patients, thoracic surgeons across the globe have adopted a variety of measures for VTE prophylaxis. Our home institution of Boston Medical Center, for example, implements a tailored version of the Caprini RAM in the management of all post-surgical patients, with prophylactic anticoagulation extending into the post-discharge period in select high-risk patients. Other thoracic surgery services chose to prevent VTE events via inpatient-

only anticoagulation, limiting outpatient VTE chemoprophylaxis for reasons such as cost to the patient, risk of anticoagulant adverse effects, and lack of tangible guidelines specific to the topic. Public-access programs such as Johns Hopkins' VTE Prophylaxis Algorithm for Hospitalized Surgery Patients, developed by The Johns Hopkins Venous Thromboembolism Collaborative, provide caregivers with user-friendly guidelines to assess VTE risk and determine proper mechanical interventions and chemoprophylaxis dosing.[24] Still, many institutions continue to rely on locally developed protocols and attending-specific preferences regarding postoperative VTE prophylaxis management. While the heterogeneity of practices regarding VTE prevention within the field of thoracic surgery does not preclude the advancement of patient safety and clinical efficacy, this lack of standardization certainly leads to difficulties in the development of general guidelines for VTE prophylaxis within our specialty. Regardless of an institution's preferred type of VTE chemoprophylaxis, individual thoracic surgery services must continue to strive towards the goal of full compliance with the timely and complete administration of postoperative anti-coagulation.

Anticoagulation in VTE prophylaxis

Perioperative anticoagulation has become a standard of care in US surgical institutions. Whether an anticoagulant agent is administered immediately prior to surgery, following the operation, or on a daily basis during postoperative hospitalizations, there is widespread agreement that some form of prophylaxis should be implemented for the prevention of VTE occurrence in postoperative patients. Still, the exact onset, duration, frequency, and choice of anticoagulation agent are inconsistent across the field of thoracic surgery. Unfractionated heparin is commonly used for VTE prophylaxis in the perioperative period. Despite low-cost and a long track record of clinical use, heparin has its disadvantages as administration requires multiple unpleasant subcutaneous injections and is reserved for inpatient use only due to the risk of developing life-threatening heparin-induced thrombocytopenia (HIT). LMWH is another agent of choice for postoperative VTE prophylaxis. With convenient once-daily subcutaneous administration and lower risk of HIT compared to unfractionated heparin, in addition to the ability to be self-administered by patients, LMWH is preferred for use in the outpatient setting.[25] Higher costs and contraindication in patients with compromised renal function can deter certain clinicians from utilizing LMWH for the purpose of VTE prophylaxis. The vitamin K antagonist warfarin is another, sparsely used option for postoperative anticoagulation. While warfarin is widely used in clinical practice for prevention of arterial emboli formation in atrial fibrillation patients, its delayed therapeutic effect, paired with need for frequent laboratory monitoring and risk of skin necrosis make it an uncommon perioperative VTE prophylactic agent.

With the development of direct oral anticoagulants (DOACs), mainly direct factor Xa inhibitors and direct thrombin inhibitors, new options have become available to clinicians for both VTE prophylaxis and treatment. FDA-approved agents such as rivaroxaban, apixaban, and dabigatran have the advantages of oral administration, which can relieve injection fatigue in patients necessitating prolonged VTE prophylaxis, and importantly, do not require laboratory monitoring with prophylactic dosing. Several clinical trials are currently investigating DOACs in both

medical and surgical patient populations, specifically in the area of orthopedic surgery where postoperative VTE development is a known and frequent complication.[26, 27, 28]

Ultimately, the combination of potentially prohibitive costs, difficult therapeutic reversal, and the lack of historical evidence-based data currently make DOACs rare VTE prophylactic agents in the postoperative period, especially when well-known and clinical trial-proven drugs such as unfractionated heparin and LMWH are available. Still, as new agents such as betrixaban are approved for VTE prophylaxis by the FDA and research efforts continue to frame the best clinical use of DOACs, clinicians are hopeful that improved drug profiles and patient-friendly administration will help simplify and ultimately standardize VTE prophylactic protocols.[29]

Summary

While considerable progress has been made in identifying thoracic surgery patients with high risk for developing post-operative VTE, the practice variation and lack of consensus regarding methods of risk stratification and VTE prophylaxis serve as major impediments to improving clinicians' capacity to prevent thromboembolic complications. To this day, salient questions remain unanswered in the pursuit of optimal post-operative VTE prevention in thoracic surgery: how best to risk stratify patients, which patients to screen for VTE occurrence, which pharmaceutical interventions to employ to prevent VTE in high-risk patients, and the exact duration of said interventions.

The incorporation of VTE RAMs into some institutional practices has enhanced clinicians' ability to identify patients at high risk for post-operative VTE in a variety of surgical fields, including thoracic surgery.[1] However, when compared to other surgical specialties, thoracic surgery has little medical literature available validating one RAM over another. Still, the Caprini RAM, including its commonly used modified versions, has proven useful when incorporated into the end users' electronic medical records (EMR). After the integration of the Caprini RAM into the EMR in the general and vascular surgery services at Boston Medical Center, Cassidy and colleagues reported a substantial reduction in post-operative VTE complications.[21] However, factors including inexperienced users, calculation errors, selection of inappropriate risk factors for score calculations, and noncompliance of patients receiving outpatient prophylaxis can lead to incorrect duration of anticoagulation and associated adverse sequelae despite an EMR-backed RAM platform. Developing automated, real-time calculations of risk scores populated by items in a patient's chart should be considered to help eliminate human error related to manual data input. Automated EMR reminders regarding VTE prophylaxis for high risk patients throughout patient admission could also help increase provider adherence to protocol.

One major factor influencing the adoption of any new protocol is its impact on the practice habits of surgeons and clinicians, especially with regard to adherence and feasibility. In a 2013 study assessing the efficacy of implementing a standardized VTE prevention protocol in a large tertiary care facility, provider adherence to the new protocol was assessed.[21] Provider practice was considered to be compliant only if the prescribed prophylactic measures fully matched the type and duration of prophylactic measures suggested by the protocol. The trend in provider adherence to protocol-driven prophylaxis recommendations was highest for patients determined to be low and moderate risk for VTE (100% adherence),

but dropped to 89% adherence in high-risk patients. Surgeon discretion and contraindications to anticoagulation explained the 11% drop in adherence for the high-risk group.[21] This trend is not surprising as the prophylactic measures recommended by the protocol for the low through moderate risk groups did not involve any additional post-discharge measures. The highest-risk groups, according to the protocol implemented in the study, involved VTE chemoprophylaxis for a period of 30 days post-surgery. Providers were permitted to deviate from the protocol-driven recommendations on a case-by-case basis with appropriate documentation supporting the reasoning for deviation. Examples of clinical protocol deviation include ambulatory operations for which VTE prophylaxis was not indicated, history of HIT, use of warfarin, and administration of platelet function-modifying agents including clopidogrel. Despite the reduced adherence rates in high-risk patients, post-operative VTE rates dropped by 84% after implementation of the protocol.[21] This analysis of physician adherence to an EMR-embedded VTE prophylaxis protocol demonstrated that strong adherence to a multifaceted, complex protocol is feasible, while simultaneously generating positive outcomes for patients. Despite the current lack of consensus on optimal risk stratification and VTE prophylaxis methods in thoracic surgery, utilization of an individual risk-based protocol has already shown promising results and warrants further investigation within the field.

Another important factor to consider is the economics of implementation of VTE-risk stratification protocols. Development and endorsement of a standardized post-operative VTE risk stratification and prophylaxis method by field-specific societies could represent the catalyst needed for institutions to innovate logistical and financial solutions required for successful implementation. Economic concerns are not limited to institutions but also extend to patients themselves. In the scenario where a patient is prescribed a protocol-recommended extended period of post-operative prophylactic anticoagulation to be completed on an outpatient basis, the possibility of insurance non-coverage can hinder patient compliance and ultimately, outcomes. Analysis of the requirements and nuances of insurance coverage are beyond the scope of this review, yet financial-driven factors can undoubtedly limit the post-operative VTE prophylaxis efforts.

A major barrier to development of thoracic surgery-specific VTE risk stratification is a lack of robust field-specific data demonstrating the clear benefit of one RAM over another. Validation and optimization of a post-operative VTE risk stratification process would allow for easier implementation, and greater inter-institutional agreement on best practices. Determining the appropriate agent for VTE prophylaxis also plays a role in complicating the decision-making surrounding VTE prophylaxis. Unfractionated and LMWH, principally enoxaparin, are routinely used for VTE prophylaxis, each having their own advantages and disadvantages. Unfractionated heparin is commonly used in the inpatient setting thanks to a long historic track record, reasonable efficacy, low cost, and relatively easy reversibility. Downsides of heparin administration, beyond the expected risk of bleeding associated with all anticoagulants, includes HIT and a significant amount of clinician and nursing time spent monitoring and administering scheduled doses. The longer half-life of LMWH allows for once per day dosing regimens that can be accomplished by patients themselves in an outpatient setting. Another benefit of LMWH is the far lower

risk of developing HIT when compared with unfractionated heparin.[25] Downfalls of LMWHs include required patient education for proper use and technique of self-injections, which increases amount of clinician or nursing time spent per patient, as well as decreased patient compliance. Additionally, LMWHs are less easily reversed with protamine sulfate. Novel oral anticoagulants, including the direct factor Xa inhibitors and thrombin inhibitors, could potentially greatly simplify VTE prophylactic measures, particularly in the event that reliable reversal agents are developed and FDA approved. Although sufficient data supporting the use of NOACs in VTE prophylaxis is not yet sufficient to drive a paradigm shift, evolution of in- and outpatient anticoagulation regimens is anticipated as the body of evidence builds over the upcoming years.

Finding the balance between extended post-surgical anticoagulation and mitigating bleeding risk is an important and difficult factor to standardize. In thoracic surgery patients at moderate and high risk for post-operative VTE, the benefit of VTE prevention through prophylaxis with LDUH or LMWH outweighs the risk for adverse bleeding events according to the 9th edition of the ACCP guidelines.[6] These guidelines do not address the concerns associated with extended post-operative prophylactic anticoagulation. In a 2017 meta-analysis of risks and benefits of VTE chemoprophylaxis for surgical patients across all specialties individually risk stratified for VTE using the 2005 Caprini score, Pannucci and colleagues report that there is no significant association between bleeding risk and Caprini score.[30] The same meta-analysis also reveals that, at the population level, only patients with Caprini scores >7 (high-risk) had significant VTE risk reduction with chemoprophylaxis, while those with Caprini scores <6 did not. In the high-risk patients provided chemoprophylaxis, there was a significant reduction in VTE without a significant increase in bleeding events.[30] However, the meta-analysis of pooled data at the population level suggests that chemoprophylaxis provided to patients with Caprini scores <7 has an unknown risk to benefit ratio, and may possibly lead to increased clinically significant bleeding events.[30]

While laying a strong foundation for postoperative management of VTE prevention, the 9th edition ACCP guidelines do not provide insight into the appropriate duration of prophylactic anticoagulation, nor do they specifically recommend use of a particular RAM for VTE risk stratification in thoracic surgery. Similarly, there currently are no professional society endorsements of a particular VTE risk stratification tool within the field of thoracic surgery. The lack of thoracic surgery-specific guidelines and standardization leads to practice variations that inevitably result in post-operative VTE events that may have otherwise been prevented. Given evidence suggesting that 2005 Caprini scores >7 have proven VTE risk reduction with protocol-recommended chemoprophylaxis, should moderate and lower risk patients continue to receive VTE prophylaxis?[30] Proponents of rigorous protocol adherence might support continued VTE prophylaxis in low- and moderate-risk patients, especially given the reported low incidence of adverse bleeding events, and risk vs. benefit of a low-cost intervention compared to the costly, life-threatening event of a PE.[6] However, the meta-analysis of VTE prophylaxis at the surgical population level suggests that prophylactically anticoagulating lower-risk patients may lead to more harm than previously anticipated.[30] Others may advocate towards a reduction of aggressive VTE prophylaxis in low-risk post-operative patients in an attempt to minimize

unnecessary interventions and adverse events, reduce hospitalization cost, and simplify the RAM protocol. More extensive data investigating thoracic surgery-specific utilization of a particular RAM along with recommendations for choice and duration of post-surgical chemoprophylaxis would support the adoption of a field-wide consensus endorsed by professional societies. With fluctuations in local pharmaceutical costs and variations in patient insurance coverage throughout the nation, developing a successful predictive model in the dynamic and heterogeneous healthcare landscape will continue to be a tremendous challenge for the foreseeable future. Still, these unanswered questions provide exciting opportunities to enhance patient safety and further clinical discovery, and can aid in the unification of post-operative VTE prevention practice within the field of thoracic surgery.

Conflict of Interest:

Jesse Schacht, Helene Sterbling, and Virginia Litle have no conflicts of interest to disclose.

Table-1. Caprini venous thromboembolism risk factors.

1 point per risk factor	2 points per risk factor	3 points per risk factor	5 points per risk factor
Age 40-59 years Minor surgery planned BMI ≥ 25 kg/m2 History of prior major surgery (<1 month) Swollen legs (current) Varicose veins Sepsis (<1 month) Serious lung disease (pneumonia) Abnormal pulmonary function (COPD) Acute myocardial infarction (<1 month) Congestive heart failure (<1 month) History of IBD Medical patient currently at bed rest **For women only:** Pregnant of post-partum History of unexplained or recurrent spontaneous abortion Oral contraceptives or HRT	Age 60 – 74 years Arthroscopic surgery Major open surgery (> 45 minutes) Laparoscopic surgery (> 45 minutes) Malignancy (present or previous) Confined to bed (>72 hours) Immobilizing plaster cast (<1 month) Central venous access	Age ≥ 75 years History of VTE Family history of VTE Positive Factor V Leiden Positive Prothrombin 20210A Positive Lupus anticoagulant Elevated anticardiolipin antibodies Elevated serum homocysteine Heparin-induced thrombocytopenia (HIT) Other congenital or acquired thrombophilias	Stroke (<1 month) Elective major lower extremity arthroplasty Hip, pelvis, leg fracture (< 1 month) Acute spinal cord fracture or paralysis (< 1 month) Multiple traumas (< 1 month)

BMI: Body Mass Index
IBD: Irritable Bowel Disease
HRT: Hormone Replacement Therapy
COPD: Chronic Obstructive Pulmonary Disease

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