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FORUM

Implementing guidelines to prevent cancer associated thrombosis: how can we do better?

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1 | INTRODUCTION

Societal guidelines addressing the prevention of venous thromboembolism (VTE) in ambulatory patients with cancer are numerous [1]. The need for guidelines is driven by an increased risk of VTE among patients with cancer (with 70% to 80% of events occurring in the outpatient setting) and the high cost of VTE management in this patient population, including decreased quality of life, increased bleeding, and early mortality in some cases [2]. Importantly, the incidence of VTE in patients with cancer is increasing in parallel with the increased number of patients living with cancer [3]. The prevalence of ambulatory patients with cancer is only expected to rise in the next several decades while literature is beginning to highlight the wide gap between guideline recommendations and practice.

2 | How are we doing?

Guidelines offer the benefit of facilitating the implementation of evidence into practice, but these benefits are not consistently seen across multiple fields of medical practice and has led to the field of implementation research [4]. Limited data is available to assess uptake of guidelines in the prevention of cancer associated thrombosis and current studies involve larger academic centers or centers with a strong hematology presence. We have reported an initial rate of guideline adherence for conducting a VTE risk assessment for patients with cancer beginning outpatient therapy at <5%, a number subsequently confirmed in 2 community oncology practice settings [5]. Others have seen similar numbers with the Association of Community Cancer Centers survey reporting <5% to 9% of patients routinely receiving standardized risk assessment and only 9% of patients at the highest risk of VTE receiving anticoagulation prophylaxis [6]. Martin et al. [7] reported that none of the high-risk patients received an anticoagulant prescription for prophylaxis and over 90% of surveyed oncologists reported rarely or never performing VTE risk assessment. The lack of VTE risk assessment, particularly in the outpatient was similarly found in a 2021 survey [8]. Similarly, in 2 studies in the community practice setting that deployed an implementation model developed at the University of Vermont, we found that although the risk assessment can be relatively straightforward to address, the actual prescribing of prophylaxis is more difficult and remained at only 25% of high-risk patients receiving prophylactic anticoagulation.

3 | WHAT'S BEHIND THE IMPLEMENTATION GAP?

Although we have limited data to comprehensively understand the implementation gap for VTE prophylaxis in cancer outpatients, several themes emerge. Importantly, patient factors are severely

understudied and compliance rates with prophylaxis in this patient setting are essentially not known. Limited data suggest that patient acceptance of VTE prophylaxis is relatively high (>90% in our data) but adherence at home, the percentage of patients limited by co-pay/out of pocket costs, and prescription refill are not available. Additional areas that mirror standard implementation barriers seen in all medical fields include provider factors, external factors, and guideline content.

3.1 | Provider factors

Major gaps in provider knowledge and provider time constraints have been identified by our research as a barrier to guideline implementation. This finding is not surprising given that the tasks required from oncology providers are essentially highly hematology focused and often nuanced (eg, an evidence-based discussion weighing the risks vs. benefits of VTE prophylaxis).

Major knowledge gaps identified for providers in our studies include:

1. Knowledge gaps related to the standardized thrombosis risk scores such as the Khorana Score.
2. Lack of familiarity with bleed risk assessment tools.
3. Lack of knowledge of how to incorporate concurrent medications such as aspirin and other anti-platelet agents in the assessment.
4. Lack of familiarity with direct oral anticoagulant options and dosing.

Additional provider factors include concerns regarding duration of anticoagulation and timing/parameters for dose adjustments, time constraints related to increased education needed, risk assessment, and patient education as well as a fear of bleeding.

3.2 | Guideline factors

Guidelines for the prevention of VTE in cancer outpatients are available from at least 5 major oncology and hematology organizations (Table) [9–13]. Guidelines share in common 4 core recommendations:

1. VTE risk assessment using a standardized risk assessment tool.
2. An assessment of bleeding risk for withholding prophylaxis in high-risk patients.
3. Initiation of prophylaxis in high-risk patients (often including incorporation of patient preference).
4. Avoiding routine prophylaxis in all patients.

3.2.1 | Guidelines differ in 3 major areas:

1. Strength of recommendations (consider, suggest, is indicated, is not recommended).
2. Recommended (or possible) drug options for prophylaxis.
3. Recommendations for intermediate risk patients.

3.2.2 | Guidelines do not address:

1. Method for bleeding risk assessment.
2. Incorporation of previous history of bleeding or thrombosis.
3. Duration of prophylactic anticoagulation.
4. Parameters for dose adjustment of prophylactic anticoagulation.

Although the core recommendations align, missing components from guidelines as well as differences in guidelines likely contribute to the lack of guideline implementation success.

3.3 | External factors

External factors that influence VTE prophylaxis guideline implementation are largely comprised of financial issues and time constraints impacting productivity and clinic flow. More research is required to investigate the financial impact of thromboprophylaxis on patients in the cancer setting (such as co-pays, insurance coverage/denial, and preferred drugs covered), but results will clearly vary across countries and health care systems. Recent publications reporting cost-effectiveness of prophylaxis suggest that it will be cost saving across different health care systems, but only among higher-risk patient populations and with the use of lower-cost agents [14–17].

Time constraints include limited face-to-face time with patients, an overburdened oncology workforce, and the need for significant upfront and ongoing hematology education. This is of particular concern in small or rural oncology practices with limited resources for information technology infrastructure and implementation of practice flow changes. The incorporation of risk assessment in the electronic health record (EHR) is likely to be associated with an improvement in risk assessment rates but no common EHR materials are available to the practicing oncologist.

4 | IMPROVING VTE PROPHYLAXIS IN AMBULATORY PATIENTS WITH CANCER

Continued research in the area of VTE prophylaxis implementation is needed to improve patient outcomes and prevent unnecessary morbidity and mortality. We can do better than a <5% to 10% implementation rate. What is unique about VTE prevention in ambulatory patients with cancer and how can we address that as a hematology community in collaboration with our oncology colleagues?

An important observation, made in our work that began in 2014, is the distinction between the 2 steps involved in VTE prevention guideline adherence: 1) risk assessment using a standardized tool and 2) the prescribing of prophylaxis to high-risk patients. Each step requires its own optimization moving forward as it is doubtful that a single step process will be identified in the near future given the competing thrombosis and hemorrhage risk in ambulatory patients

TABLE Guidelines at- a- Glance: Prevention of Cancer Associated Thrombosis in Ambulatory Patients with cancer Initiating Systemic Therapy. Major societal guidelines available in the published domain and updated in the last 4 y. Where direct oral anticoagulant therapy is recommended, all guidelines recommended apixaban or rivaroxaban as options. A free app is available for download for the International Initiative on Thrombosis and Cancer guidelines.

	ISTH [9]	ASCO [10]	ASH [11]	International Initiative on Thrombosis and Cancer [12]	SEOM [13]
Patient groups with prophylactic anticoagulation recommended	KRS ≥ 2- DOAC recommended LMWH can be considered if DOAC contraindicated	KRS ≥ 2- LMWH or DOAC may be offered	High risk of VTE- DOAC or LMWH recommended Intermediate Risk of VTE DOAC- conditional recommendation	KRS ≥ 2- DOAC recommended	KRS ≥ 2- LMWH or DOAC may be considered
		Multiple myeloma patients receiving -imid therapy with chemotherapy and/or dexamethasone – low risk patient- ASA high risk patient- LMWH should be offered-	MM patients receiving -imid based regimens- Aspirin, fixed dose VKA or LMWH is suggested	Immunomodulatory drugs combined with steroids or other systemic therapy- VKA (low or therapeutic dose) prophylactic LMWH or low dose ASA recommended	
				Locally advanced and metastatic pancreatic cancer patients- LMWH or DOAC recommended	Advanced pancreatic cancer, NSCLC with ROS-1 or ALK rearrangement or considered high-risk based on a validated RAM- LMWH or DOAC may be considered
VTE risk assessment	Recommendations based on use of Khorana Risk Score	Risk adapted approach recommended	Recommend classification of patients as low-, intermediate-, or high-risk for VTE based on a validated risk-assessment tool (ie Khorana score) complemented by clinical judgement and experience	Recommended – provides examples of multiple validated models	Recommended at initiation of therapy and during evolution of treatment and disease A validated risk assessment model is recommended

(Continues)

TABLE (Continued)

	ISTH [9]	ASCO [10]	ASH [11]	International Initiative on Thrombosis and Cancer [12]	SEOM [13]
Recommendations regarding duration of prophylactic anticoagulation	Suggest for up to 6 mo after initiation of therapy with monitoring of platelet counts and risk of bleeding complications	No specific recommendations	No specific recommendations	No specific recommendations	No consensus on duration but suggested at least 12 wk after initiation of new systemic therapy Recommend drug-drug interaction assessment
Bleeding risk assessment and considerations	Not directly addressed but highlights trials excluded patients with platelet count < 50,000/mm^3 or creatinine clearance < 30 mL/min and sites the location of bleeding in DOAC prophylaxis trials mainly in gastrointestinal tract as a consideration	No specific recommendations for assessment States VTE prophylaxis can be considered if no significant risk factors for bleeding and no drug interactions	No specific recommendations for assessment "Thromboprophylaxis should be used with caution in those with a high risk of bleeding"	Estimate bleeding risk level using bleeding risk factors: prior bleed, hepatic or renal disease, ethanol abuse, malignancy, age >75 y, reduced platelet count or function, hypertension (uncontrolled) Not actively bleeding and not at high risk of bleeding Sites the CAT-Bleed Score	No specific recommendations for assessment States patients should have "No contraindications to anticoagulation and low risk of bleeding" Monitor patients receiving primary thromboprophylaxis closely
Additional considerations and recommendations	Suggest prophylaxis if no contraindications or drug interactions Consider patient preferences and values	Suggest discuss with patient relative risks and harms; drug cost and duration of therapy	Decisions should be based on patient's individual risk for thrombosis and major bleeding Acknowledges drug availability and approval may vary across settings	Prophylaxis NOT recommended for locally advanced or metastatic lung cancer Only consider DOACs in patients who do not have GI absorption impairment, are not actively bleeding or a high risk of bleeding and who have no potential drug-drug interactions	Recommendation to educate patient regarding VTE risk factors and early symptoms at time of cancer diagnosis and during cancer evolution

DOAC, direct oral anticoagulant; GI, gastrointestinal; KRS, Khorana Risk Score; LMWH, low molecular weight heparin; MM, multiple myeloma; ASA, aspirin; VKA, vitamin K antagonist; -imid, immunomodulatory therapy.

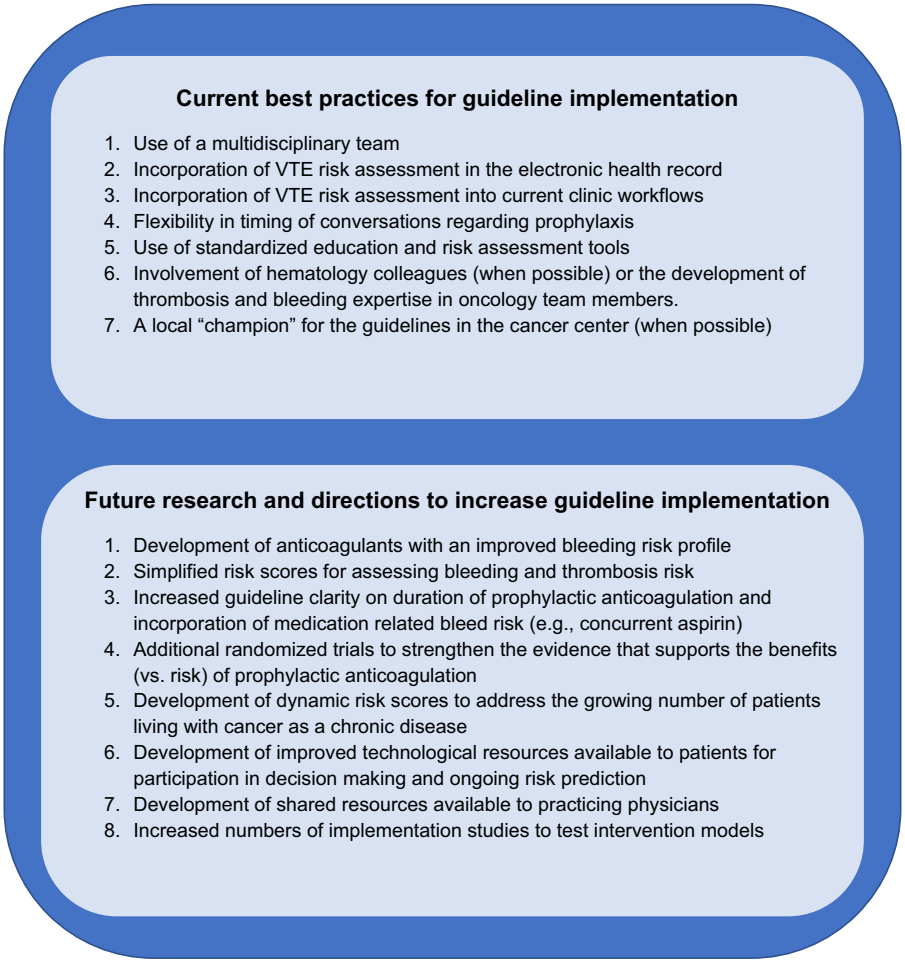

FIGURE Prevention of VTE in ambulatory patients with cancer: Best practices and future directions

with cancer. Others have questioned the use of a "pan-cancer" risk prediction score and suggested refinements are needed to reduce the patient numbers needed to treat to prevent one VTE [18].

The current best practices known for implementation of VTE prophylaxis in ambulatory patients with cancer are found in the Figure and largely derive from limited studies [5, 19, 20]. Areas to be addressed by the research and clinical practice community that might improve guideline uptake are also found in the Figure. Innovative solutions that reduce and/or better predict bleeding risk, increase provider and patient education, support the development and validation of the simplest and most effective risk assessment tools and the availability of materials to support EHR implementation are needed.

To this end, we are uploading the current University of Vermont program to the common community library in the EPIC EHR for general access to all practices and this can also be found in the supplementary materials. Additionally, basic handouts that can be adapted are under development from the North American Thrombosis Forum. Ultimately, the most impactful practice guidelines are those that benefit the largest number of patients. As we move research forward and update guidelines in the prevention of VTE in ambulatory patients with cancer, continued assessment of guideline uptake rates are needed.

AUTHOR CONTRIBUTIONS

Chris Holmes conceived of, wrote, and edited the manuscript and figures.

Steven Ades edited the manuscript and contributed to figures.

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