A literature review of venous thromboembolism prophylaxis in cancer patients using direct oral anticoagulation

Mark Shawarsky, PA-S, BSc, B.Ed., BSc (Pharm)

Student #6800783

umshawam@myumanitoba.ca

Mentor: Rebecca Mueller, PA-C, MSc

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Abstract

Introduction: Venous thromboembolism (VTE) risk is four to seven times greater in cancer patients than the general population and is the leading cause of morbidity and mortality among such patients receiving chemotherapy. Direct oral anticoagulants (DOACs) have become a standard of care along with low molecular weight heparins (LMWHs) for the treatment of VTE in non-cancer patients. Recent studies have investigated prophylactic DOAC use for cancer patients and have provided the first evidence of benefit for certain high-risk patients.

Objective: This literature review reviewed available evidence to determine whether DOACs are acceptable alternatives to LMWHs for VTE prophylaxis in cancer patients and if certain patient characteristics would preclude their use in this population.

Methods: This review searched the PUBMED and MEDLINE databases for papers of relevance published in the past decade that addressed the research question using search terms related to DOACs, VTE, cancer and prophylaxis. Three phase 3 clinical trials were identified using this approach and a further phase 2 clinical trials was found via manual reference list review of the yielded results.

Results: The two phase 3 trials conducted in ambulatory cancer patients comparing the DOACs apixaban and rivaroxaban to placebo demonstrated modest to limited benefit of DOAC use for prophylaxis in intermediate to high-risk patients based on previously validated risk assessment scores. Major bleeding events were primarily clustered in those with gastrointestinal (GI) and gynaecological malignancies, though overall events were in keeping with LMWH trials conducted previously. The third phase 3 trial comparing a DOAC to a LMWH was unhelpful in answering our clinical question as, among the numerous issues uncovered with the trial, it included patients with a past cancer history, rather than active cancer, as the majority of the cancer subgroup.

Conclusion: When utilizing a validated risk assessment score in cancer patients, the DOACs apixaban and rivaroxaban appear to be equally valid options to LMWHs for VTE prophylaxis in cancer patients. The precise context and clinical role of this intervention would best be clarified by dedicated phase 3 trials comparing LMWHs to DOACs in intermediate to high-risk cancer patients. No patient characteristics have shown to be conclusively at a higher risk of major bleeding, but future trials should consider creating a sizable GI and gynaecological malignancy subgroup for further elucidation.

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Introduction

Venous thromboembolism (VTE) risk in cancer patients is four to seven times greater than the risk among the general population.(1) VTE among cancer patients not only interferes with cancer treatment, but is also the leading cause of mortality and morbidity among cancer patients receiving chemotherapy.(2) VTE, which consists of deep vein thrombosis and pulmonary embolism, is the consequence of neoplasms leading the human body to be in a hypercoagulable state secondary to the production and release of procoagulant proteins, inflammatory cytokines, as well as procoagulant particles from host cells and tumour cells alike.(3) In 2013, it was calculated that within the first year of a cancer diagnosis, approximately 8% of patients go on to develop VTE.(1) It is estimated that among all cancer patients, 30% will go on to have an occurrence of VTE.(4) With these data known by primary care providers, including physician assistants, it is of great clinical interest to determine what, if anything, can be done to avoid or forestall such outcomes in newly diagnosed cancer patients.

Broadly available anticoagulants for VTE prophylaxis include heparins, low-molecular weight heparins (LMWH), vitamin K antagonists such as warfarin, and novel or direct oral anticoagulants (DOACs). The use of low molecular weight heparins for the prophylaxis of certain high risk cancer patients has now made its way to clinical practice guidelines, though routine use in all ambulatory cancer patients is still not recommended.(5) There have been numerous studies and two particularly high profile large scale randomized control trials (RCTs) within the past decade showing decreased VTE incidence without notable increased risk of major bleeding in chemotherapy receiving cancer patients.(6,7) However, making LWMH a standard prophylactic recommendation for all cancer patients is hampered by systematic reviews demonstrating a number needed to treat (NNT) of 30 and non-statistically significant relative risk (RR) of major bleeds of 1.44 combined with

substantial costs associated with such therapy.(8) This NNT does not compare unfavourably to other recommended interventions. For example, secondary prevention of cardiovascular complications with aspirin has a NNT of approximately 50.(9) The relative risk of bleeding is also 44% increased but, as mentioned, is not statistically significant with the 95% confidence interval (CI) ranging from 0.98-2.14. Despite these not unfavourable comparisons, concerns remain that bleeding risks may be almost twice as high as shown in the confidence interval and that more targeted therapy can lower the NNT for benefit to the mid-teens.(10) Thus, the current prophylactic standard of care with regard to VTE in cancer patients ranges from no intervention to LMWHs, depending on the cancer type and patient bleeding risk. The inclusion in guidelines (11), to the extent it has occurred, has been the result of multiple trials demonstrating efficacy for selected populations over the past decade.(8) Recent metadata have appeared to confirm that LMWHs and DOACs are superior in both efficacy and safety for VTE treatment in cancer patients; compared to Vitamin K antagonists such as warfarin.(12) However, that same data suggest that while DOACs may be more efficacious than LMWHs, they may have worse safety profiles with regard to major bleeding events, not including overall mortality.(12) Of note, the DOACs have largely become the standard of care for treatment of VTE in non-cancer patients in the past 5 years due to demonstrated efficacy, ease of use, decreased monitoring, and relative safety demonstrated in numerous trials.(13)

It is surprising, given the several advantages DOACs have over traditional VTE therapies like LMWHs and warfarin, including oral administration, simple dosing schedules, lack of need for initial parenteral injections, lack of required routine monitoring and dosage adjustments, and the small number of known drug–drug interactions, that to date, there have only been two phase 3 clinical trials looking at direct oral anticoagulant use for VTE prophylaxis in malignancy. (14,15) There has also been a single phase 2 clinical trial (16) as

well as a single RCT that was comparing DOAC to LMWH use in critically ill patients that had a large portion of cancer patients that could be separated and analyzed separately.(17,18) These trials have looked specifically at rivaroxaban, apixaban and betrixaban. No trials have used dabigatran, or edoxaban to study VTE prophylaxis in malignancy. This is an especially salient point with regard to dabigatran, as it is the only DOAC of its mechanistic type on the market.

DOACs Mechanism of Action

The DOACs approved for use in VTE management in North America include the direct thrombin inhibitor dabigatran and four factor Xa inhibitors, rivaroxaban, apixaban, edoxaban, and betrixaban. *Figure 1* (below) illustrates where different classes of anticoagulants are acting within the clotting cascade. Dabigatran etexilate is a factor IIa (thrombin) inhibitor. It is a prodrug, which is activated by microsomal carboxylesterases found in the liver.(19) Dabigatran has over 80% renal clearance and is metabolized by P-glycoprotein. The other DOACs have varying degrees of renal clearance, ranging from 50% with edoxaban to as low as 25% with apixaban, and are also metabolized by P-glycoprotein and to various degrees by CYP3A4.(20) These DOACs are all factor Xa inhibitors and their mechanisms of action include the inhibition of prothrombinase complex-bound and clot-associated factor Xa. This reduces the thrombin burst during the propagation phase of the coagulation cascade. Additionally, platelet aggregation induced by collagen, adenosine diphosphate or thrombin is unaffected by these moieties.(20) Despite the known theoretical potential for CYP3A4 and P-glycoprotein interactions with DOAC use, the clinical significance and realistic potential for significant harmful drug-drug interactions with chemotherapeutic agents is still unknown.(21)

The major concern raised with regard to widespread DOAC use has been the lack of a specific antidote; however, with the advent of the monoclonal antibody idaricizumab to

reverse dabigatran as well as the modified recombinant factor Xa known as andexanet alfa, this may one day become a moot point. More than a decade of clinical experience has led to increasing amounts of comfort with DOAC use despite a lack of widely available antidotes. This being said, major bleeding, though present at lower rates with DOACs than with warfarin(22), has thus far been treated with clotting factor replacement known as prothrombin complex concentrate or PCC. The reversal agent idaricizumab binds dabigatran with higher affinity than thrombin and has become the antidote of choice for major bleeding associated with dabigatran in Canada.(23) Andexanet alfa, was approved in the United States for reversal of bleeding from factor Xa inhibitors in 2018 and is in the process of receiving regulatory approval from Health Canada. The mechanism by which haemostasis is achieved with this drug is by acting as a decoy receptor for factor Xa inhibitors, as the affinity for the drug is identical to the affinity for natural factor Xa.

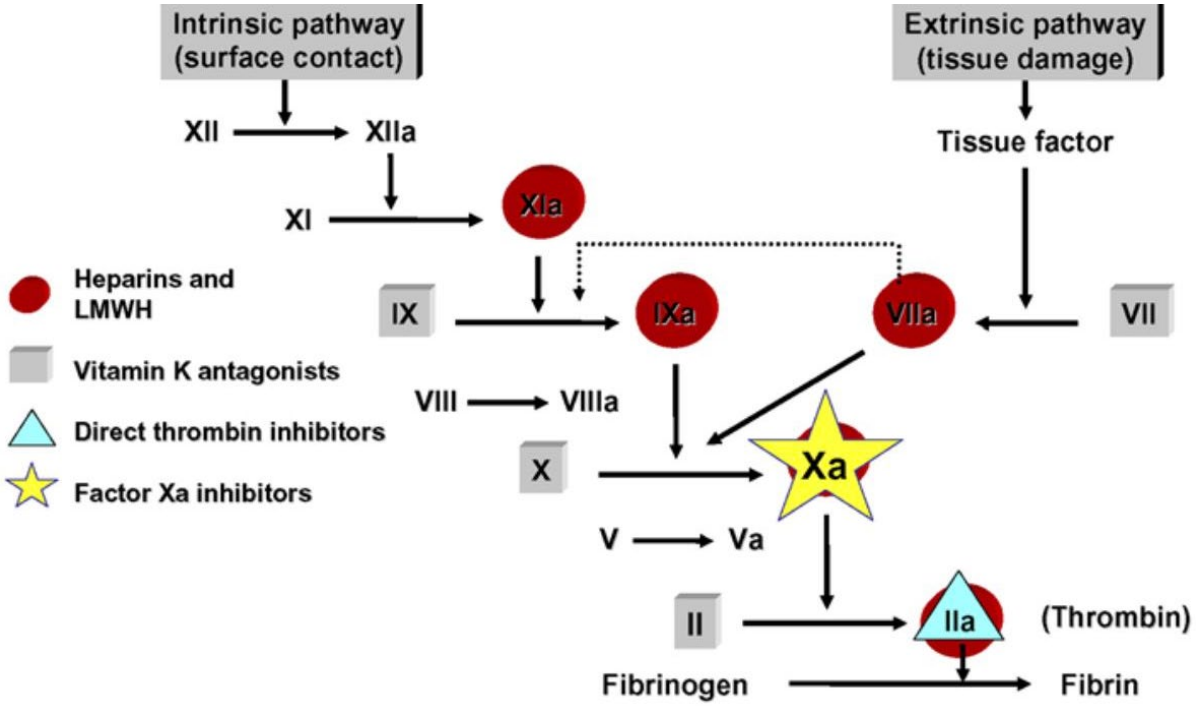

Figure 1: Areas of activity within the clotting cascade for commonly used anticoagulants(24)

Cancer VTE Risk Assessment

A number of risk-assessment scores have emerged over the past decade in an attempt to identify the highest risk patients for cancer related VTE who would most potentially benefit from thromboprophylaxis and reduce the aforementioned NNTs (ranging from 30-40) identified by systematic review of all thromboprophylaxis trials involving both LMWH and DOACs. These scores have helped identify higher risk patients who would be more likely to benefit from VTE prophylaxis than the cancer population as a whole and have been incorporated into societal guideline recommendations in an attempt to allow for very limited and specific recommendations to be made for LMWH and DOAC use in the prophylactic cancer related VTE setting.(25) Examples of such scores include the Khorana (26), Vienna CATs (27), PROTECHT (10), CONKO (28) and Compass-CAT scores (29). These scoring systems and others have been validated and look at various factors including tumour size, location, stage, type, time since cancer diagnosis and comorbidities. A constant among the scores (save for Compass-CAT) is the inclusion of white blood cell count, platelet counts, haemoglobin levels and high-risk tumour types as part of the models. Other factors that differ among the models include consideration of BMI, chemotherapy regimen, D-Dimer levels, comorbidities, and age. *Figure 2* (below) illustrates the criteria for the Khorana score, which was the risk assessment tool utilized by the two major trials analyzed in this review.(14,15)

Patient characteristics	Risk Score	0 points = Low risk
1. Site of cancer		1-2 points = Intermediate risk
Very high risk (stomach, pancreas)	2	≥3 points = High risk
High risk (lymphoma, lung, gynecologic, bladder, and testicular cancers)	1	
2. Pre-chemotherapy platelet count ≥ 350 x 10^9/L	1	2.5 month rate of VTE
3. Haemoglobin level < 10 mg/dl or the use of red cell growth factors	1	Low risk 0.3-0.8%
4. Pre-chemotherapy leukocyte count > 11 x 10^9/L	1	Intermediate risk 1.8-2.0%
5. BMI 35 kg/m^2 or more	1	High risk 6.7-7.1%

Figure 2: Khorana score: A risk assessment tool to calculate the risk of developing thrombosis in outpatients with cancer(30)

Current role of DOACs in VTE Prophylaxis Guidelines and the need for further study

Recent clinical guidance released in 2019 from the committee Haemostasis & Malignancy of the International Society for Thrombosis and Haemostasis (ISTH) has deemed that evidence is strong enough to suggest, but not recommend, that DOACs be an option for certain high risk cancer patients and they continue to suggest the use of LMWH when outside of narrowly defined parameters.(31) The American Society of Haematology has recently released new guidelines in February of 2021 related to prophylaxis and treatment of VTE in patients with cancer.(11) Their recommendations regarding VTE prophylaxis in cancer patients are included for reference (see Appendix). In summary, these guidelines are silent as to the use of DOACs for cancer patients undergoing surgery, as well as with regard to hospitalized medical patients. Recommendations for surgical cancer patients and hospitalized patients with cancer, when they do recommend thromboprophylaxis, only comment on LMWH and UFH. These recommendations remain quiet on DOAC usage due to no dedicated studies having been carried out with DOACs in surgical cancer patients and only one study that included hospitalized cancer patients receiving a DOAC, and this was only a small subgroup.(17) Suggestions and recommendations that address DOAC usage for thromboprophylaxis name rivaroxaban and apixaban exclusively. The recommendations are recorded as conditional and that the aforementioned DOACs be considered in ambulatory cancer patients receiving systemic therapy at both intermediate or high risk of VTE based on a validated risk assessment score. This contrasts with the conditional recommendation to avoid thromboprophylaxis with LMWHs in the same populations calculated to be at intermediate risk. There are no recommendations addressing the preference for use of DOAC or LMWH when both could be recommended due to no trials having ever compared the two classes in ambulatory cancer patients.(11)

Given that there is still a great deal of debate as to whether DOACs should be used for primary prophylaxis of VTE in malignancy(32) and the context within which this could be considered, there is an opportunity at hand to critically appraise the available literature and data to provide new perspectives and considerations not previously considered.

Study Thesis and Research Goals

By means of a literature review of relevant clinical trials conducted globally in the past decade, current data has been synthesized and analysed to assess whether to support the notion that direct/novel oral anticoagulants ought to be considered alongside low molecular weight heparins as good therapeutic options for the prevention of venous thromboembolism in cancer patients. The explicit goal of this undertaking has been to begin formulating potential evidence-based answers to the following clinically relevant questions:

1) Are direct oral anticoagulants acceptable alternatives to low molecular weight heparins in the prophylaxis of venous thromboembolism in cancer patients?
2) What cancer/patient characteristics would preclude the use of direct oral anticoagulation in venous thromboembolism prophylaxis?

Research design and Methodology

This literature review consists of a qualitative analysis and critique of the conducted clinical trials in the area. The University of Manitoba, Neil John MacLean Health Sciences Library, Health Sciences Librarian, Caroline Monnin MLIS, was consulted to devise search criteria and MeSH terms that would be certain to produce only papers of relevance to the research question.

To yield papers of relevance, extensive PUBMED and MEDLINE searches were conducted. Due to the paucity of data in this area searches were not limited to geographic area, nor to subtypes of cancer. Keywords include: Neoplasms, Venous Thrombosis, Venous

Thromboembolism, and Factor Xa inhibitors. The searches were designed and built as follows: (("Neoplasms/drug therapy"[Mesh] OR "Neoplasms/therapeutic use"[Mesh] OR neoplasm*[title/abstract] OR cancer*[title/abstract] OR tumo?r[title/abstract])) AND ("Venous Thrombosis"[Mesh:NoExp] OR "Venous Thromboembolism"[Mesh] OR DVT[title/abstract] OR DVE[title/abstract] OR thromboembolism[title/abstract] OR "deep vein thrombos*"[title/abstract] OR "deep venous thrombos*"[title/abstract] AND (thromboprophylax*[title/abstract] OR prophylax*[title/abstract])) AND ("Factor Xa Inhibitors"[Mesh] OR DOAC[title/abstract] OR "direct oral anticoagulant"[title/abstract]). Exclusion criteria for the searches included only papers published in English as well as only data from the past decade; however, due to the relative novelty of the therapeutic agent class, this did not result in the exclusion of any published data in this area.

This approach generated 64 individual papers, trials, reviews, and book chapters. When further refining the search to include only systematic reviews, meta-analyses and clinical trials, there were a total of 10 generated results of which 3 were of direct relevance to the research questions. A further phase 2 clinical trial was identified by manual reference list review from the generated search results.

Results

a) ***Study Populations Included and Excluded from trials***

Critical study characteristics are described in *Table 1* (below). All of the relevant studies excluded those with prior VTE, recent bleeding history, other coagulopathy or bleeding diathesis, significant liver disease, low platelet counts, pregnancy, and end-stage renal disease (ESRD, Creatinine Clearance <30 ml/min). The AVERT trial was the only included study that did not exclude patients with primary brain neoplasms or brain metastases. The APEX trial was notable for including those with ESRD. The Levine, CASSINI, and AVERT trials

all excluded those expected to survive less than 6 months and had an Eastern Cooperative Oncology Group performance status equal or greater than 3 out of 5(signifying limited self-care and confined to bed or chair more than 50% of the time). CASSINI and AVERT patients also needed to have calculated Khorana VTE risk scores equal or greater than 2.

The APEX study had the most unique inclusion criteria and included adults over 40 years of age who had been hospitalized in the past 96 hours for at least one of the following acute medical diseases: heart failure, respiratory failure, infection, rheumatic disease, or ischemic stroke, had severe immobilization greater than 24 hours and anticipated severe to moderate immobilization greater than 3 days. Patients included in the cancer subgroup of the trial consisted of both individuals with active cancer as well as a previous cancer history. The exclusion criteria were quite numerous. The most salient were those with life expectancy less than 8 weeks, active lung cancer, and unable to receive ultrasound sonography during trial.

The CASSINI trial studied adult ambulatory cancer outpatients with solid tumors or lymphoma. The AVERT trial included adult patients with newly diagnosed cancer or progression after complete or partial remission. Notable exclusion criteria unique to AVERT were having a cancer diagnosis only of basal-cell or squamous-cell skin carcinoma, acute leukemia, or myeloproliferative neoplasm; planned stem-cell transplantation. Though, AVERT and CASSINI included patients with renal insufficiency, only 5.8% of AVERT patients had an estimated creatinine clearance between 30-50 ml/min.

b) Trial Design and Comparative Interventions

The Levine study was a placebo controlled double blinded randomized control trial that compared three groups receiving apixaban at either 5 mg, 10 mg, or 20 mg for twelve weeks with a fourth placebo-controlled group. The various dosages trialed for apixaban can be attributed to it being a very new drug at the time of the trial in 2012, and the most efficacious

and safe dosage ranges were not yet well established. All groups were followed throughout the treatment phase and 30 days after the twelve-week treatment to assess efficacy and safety endpoints. In total, there were 125 patients who completed the trial; split evenly amongst the 4 groups. This represented 78% of patients receiving apixaban and 63% of patients receiving placebo.

APEX was a randomized, double-blind, double dummy multi-centre randomized control trial that compared 35-42 days of Betrixaban (with an initial loading dose) to 10-14 days of VTE prophylaxis dosing of enoxaparin. The double dummy approach involves both arms of a trial receiving placebo of the other group's treatment. This ensures that blinding is not compromised when two different treatment types are used. Injections and capsules in this instance. A subgroup (n=959) of the larger phase 3 APEX trial had either a previously described non-excluded active cancer or history of cancer. Of those patients in the cancer subgroup, 499 received Betrixaban and 460 received Enoxaparin. Efficacy and safety were assessed at the end of the 7-week trial for both populations.

CASSINI was a randomized, double blind, parallel group, placebo controlled, multicentre study comparing daily rivaroxaban to placebo. In parallel group studies, participants are assigned randomly to a treatment protocol, which in this case was either treatment with rivaroxaban or treatment with placebo. The study concluded with 841 patients who were included in the intention to treat efficacy analysis and 809 patients were included in the safety analysis. The reason for the disparity in those numbers is attributable to including all randomized patients in the efficacy analysis but only including patients who ended up receiving at least one dose of either placebo or rivaroxaban in the safety analysis. The trial was designed to last 180 days, with efficacy endpoints assessed within 3 days of the end of that time or at the end of intervention. Screening ultrasounds were performed initially

to rule out pre-existing proximal DVT and at specified intervals thereafter. Safety endpoints were assessed at 2 days after the last dose of either intervention.

The AVERT trail was a randomized, double blind, parallel group, placebo controlled, multicentre study that compared twice daily apixaban to placebo. There were 563 patients included in the efficacy and safety endpoint analyses. Patients were to be on a protocol for 180 days, and then monitored for VTE for an additional 30 days post drug completion

c) Study Primary Efficacy and Safety Endpoints

The Levine study had a secondary endpoint of symptomatic (and U/S or CT) confirmed DVT or PE, which was analogous to the efficacy endpoint of the other major trials. Its primary endpoint was a safety endpoint consisting of major bleeding or clinically relevant non-major bleeding (CRNB). Major bleed being defined using the International Society of Thrombosis and Haemostasis (ISTH) criteria as meeting one of the following: hemoglobin drops of 20 g/L, requiring blood transfusion of at least 2 units of packed red blood cells, bleeding to a pre-defined critical site, or bleeding leading to death.(33) CRNB was also pre-defined using ISTH criteria, and essentially encapsulates bleeding deemed clinically relevant by a physician or patient; this would include that which requires medical intervention, leading to hospitalization or increased care, or prompting face-to-face evaluation.(34) These safety endpoints were also utilized by the APEX, AVERT and CASSINI trials. Efficacy endpoints for those trials each included imaging confirmed DVT or PE. The only discrepancy being that the AVERT trial did not include distal DVT in its outcome.

d) Endpoint frequency

Occurrence of DVT and PE in the Levine trial, which was analogous to the other trials' primary efficacy endpoint but were defined as a secondary safety endpoint within the study. There were no occurrences within any apixaban cohort and 3 such instances (10.3% of

patients) in the placebo grouping. The APEX study did not demonstrate a difference between betrixaban or enoxaparin with regard to major VTE prevention in the cancer subgroup (Betrixaban 5.7% vs. Enoxaparin 6.2%, RR 0.99, 95% CI 0.59–1.64, p = 0.95), whereas a statistical advantage was found in favour of betrixaban among the much larger non-cancer trial patients (Betrixaban 4.2% vs. Enoxaparin 6.0%, RR 0.71, 95% CI 0.57–0.88, p = 0.002). There was no significant interaction found on the primary outcome irrespective of cancer status (interaction p = 0.36). Within the CASSINI trial the primary efficacy endpoint occurred in 8.8% of the placebo arm (37 patients) and 6.0% of the rivaroxaban arm (25 patients) during the 180-day trial period. This resulted in a hazard ratio (HR) of 0.66 with a 95% confidence interval 0.4 – 1.09 with p = 0.1. However, during the intervention period the endpoint occurred in 2.6% of patients on rivaroxaban and 6.4% on placebo, HR 0.40; 95% CI, 0.20–0.80. The primary endpoint of major VTE in the AVERT trial occurred in 12 patients (4.2%) of the apixaban grouping and in 28 patients (10.2%) of the placebo group. This resulted in a HR of 0.41 and a 95% CI of 0.26 – 0.65 and p =<0.001.

Within the Levine trial major bleeds occurred in 3.4 % (1 patient) of the placebo cohort and in 6.3% (2 patients) of the 20 mg apixaban cohort; with none occurring in the other apixaban arms. CRNM bleeds did not occur within the placebo group and occurred in 3.4% of both the 5 mg and 10 mg apixaban groups and in 6.3% of the 20 mg apixaban section. The primary safety endpoint of major bleed and CRNB occurred in 2.9% of the betrixaban group and 2.0% of the enoxaparin group (RR 1.43, CI 0.63–3.27, p = 0.40). This was non-significant, but it should be noted that among non-cancer patients there was no significant difference between rates of major bleeding between groups, but a significant difference in favor of enoxaparin with regard to CRNB (RR 2.07, CI 1.48-2.89, p = <0.001). Major bleeding in CASSINI occurred in 1.0% of the placebo arm and 2.0% of the rivaroxaban arm for a HR of 1.96 but a CI of 0.59 – 6.49 and p = 0.26. The secondary safety endpoint of

CRNB occurred in 2.0% of the placebo arm and 2.7% of the rivaroxaban arm. This also lead to a HR of 1.34 but a CI of 0.54 – 3.32 and p = 0.53. The primary safety endpoint of major bleeding in the AVERT trial using modified intention to treat analysis occurred in 10 patients (3.5%) of the apixaban arm and 5 patients (1.8%) of the placebo grouping. This lead to a HR of 2.00 and 95% CI of 1.01 – 3.95 and p = 0.046. However, during the treatment period this endpoint occurred in 2.1% of apixaban patients and 1.1% of placebo patients. This accounted for a HR of 1.89 at a non-significant 95% CI of 0.39 – 9.24. Notably, death from any causes was not significantly different statistically between the two groups, and 87% of those who died (54 out of 62 deaths) were due to underlying cancer. Of note, 80% of major bleeds in the intervention group occurred in patients with gynecologic or GI related malignancies.

The most notable features amongst the various endpoints include the lack of events in the Levine trial. This is unsurprising due to the 3 versus 6-to-7-month trial length of CASSINI and AVERT as well as the much smaller study population. AVERT also had an event rate approximately 50% smaller than CASSINI which may partially be explained by the attenuation provided by not including distal DVT in the primary outcome. Safety events were almost doubled in AVERT compared to CASSINI, which may be related to the 46% discontinuation rate in CASSINI, that theoretically could lead to increased VTE events but decreased major bleeding secondary to no active drug being taken in such instances.

e) Adherence to trial regimen and discontinuation rates

The Levine study disclosed that 78% of the apixaban arms completed the 12-week trial (78%, 80%, 76% in each respective cohort) and 63% of the placebo arm completed the trial. It was acknowledged that the majority of discontinuation was due to the underlying cancer, but these data were not provided. However, no individuals were lost to follow up.

The APEX study used an intention to treat analysis for all endpoints but did not specify individuals lost to follow up or discontinuation rates between groups. However, it was disclosed that 15% of all randomized patients were excluded from primary analyses due to lack of follow up ultrasonography. The median duration of treatment was reported and was 36 days in the betrixaban group and 9 days in the enoxaparin group. Durations of treatment and exclusion due to lack of ultrasonography were not further broken down into subgroups (including those with active cancer).

The CASSINI trial had regimen adherence rates that averaged 98.4% in both the rivaroxaban group and placebo group. Discontinuation rates were 43.7% of the rivaroxaban group and 50.2% of the placebo group. Reasoning for discontinuation were similar among both groups and baseline characteristics of patients who did not complete the treatment regimen were not found to be statistically significant. This trial also utilized an intention to treat analysis, thus even those who did not complete the regimens were included in outcome analysis and a total of 39% of endpoint events occurred in those individuals.

Adherence rates in the AVERT trail were 83.6% in the apixaban group and 84.1% in the placebo group. A total of 19% of the placebo cohort chose to discontinue the trial and 18% of the apixaban cohort did the same. The most prevalent reasons were ‘not wishing to participate’ and undefined ‘miscellaneous’, with similar totals for both groups save for discontinuation due to VTE occurring in 22 patients in the placebo arm and 7 patients within the apixaban arm. 35 patients in the apixaban cohort died during the trial, as did 27 within the placebo cohort. The vast majority (86%) of these deaths were related to the underlying cancer, or its progression.

f) Patient cancer subtypes

The Levine study had a total of 80% of patients with solid tumors of which tumors of the breast, lung, pancreas, prostate, and colon were most prevalent. Approximately 16% of patients had hematological malignancies and just over a quarter of all patients had concomitant liver metastases. Both the Levine and APEX studies did not specify cancer types or staging, although Levine indicated that all cancers were either advanced or metastatic. As noted previously, there were no patients in the APEX trial with active cerebral neoplasms or metastases, as well as no patients with active lung cancer. It was not disclosed in the trial paper how active cancer was defined, but the post hoc cancer specific analysis conducted by Ageno et al.(17) had revealed that this included those with a history of cancer and that those individuals comprised the majority of the cancer subgroups.

Within the CASSINI trial over 70% of the 274 patients had either pancreatic (33%), gastric (21%), or lung cancer (16%). The majority of patients (54.5%) had a TMN classification of Stage IV. The primary cancer types in the AVERT trial were 25.8% gynecologic, 25.3% lymphomas, 13.6% pancreatic and 10.3% lung. TMN staging was not identified within the trial paper or supplementary appendix.

Table 1: Critical Study Characteristics

Trial Name and Year	APEX 2016 (18)	CASSINI 2019 (15)	AVERT 2019 (14)	LEVINE 2012 (16)
Intervention	Betrixaban vs Enoxaparin	Rivaroxaban vs Placebo	Apixaban vs Placebo	Apixaban vs Placebo
Population	Immobilized Inpatients	Ambulatory Outpatients	Ambulatory Outpatients	Outpatients with metastatic disease
Population Size	959 (cancer subset)	841	573	125
Primary Efficacy Endpoint	VTE/PE	VTE/PE	VTE/PE	VTE/PE
Primary Safety Endpoint	Major Bleed + CRNB	Major Bleed	Major Bleed	Major Bleed + CRNB
Efficacy % Occurances	I = 5.7% PC = 6.2%	I = 6.0% PC = 8.8%	I = 4.2% PC = 10.2%	I = 0% PC = 10.3%
Statistical Efficacy Favours	None	None	Apixaban	Apixaban
Safety % Occurances Major	I = 2.9% PC =2.0%	I = 2.0% PC = 1.0%	I = 3.5% PC =1.8%	I = 6.3%*/ 0% PC = 3.4%
Study Duration	7 weeks	6 months	6 months (Followed 7)	3 months
Notable study Details	•non-cancer cohort showed small statistical benefit toward betrixaban •cancer sub-group not well defined included patients with cancer history •many confounding medical conditions •>15% of participants not included in outcome due to poor data collection	•during intervention period Rivaroxaban did have greater statistical efficacy (I = 2.6 vs PC=6.4 , CI = 0.2-0.8) •46% drug discontinuation biased toward null hypothesis (no intervention effect)	•only study to not exclude brain mets •distal DVT not included •no statistical advantage for placebo safety during intervention,but significant VTE reduction (7.3 PC vs 1.0 I) •Bleeds cluster in GI/GYNE malignancies	•hypothesis generating Phase 2 study •4 groups and 3 strengths of apixiban • only 25% received placebo • only advanced/metastatic disease population but staging undefined
	***only at 20 mg Apixaban dose/^CRNB = Clinically Relevant Non-Major Bleed/I = Intervention PC= Placebo or Comparitor**			

Discussion

Cancer patients as well as cancers types themselves comprise such a disparate group of diseases, patient populations, and clinical situations that it should not be at all unexpected that sweeping clinical answers and pronouncements cannot often be made without being accompanied by a litany of caveats, exceptions, and non-applicable or as yet undetermined responses. This is especially true when trying to make broad generalizations about cancer patients as a whole as well as acceptable prophylaxis or treatments with respect to all types of cancers. With this context understood and established, one can begin to dissect what these specific trials have shed some light upon for clinicians to contemplate when considering VTE prophylaxis for their cancer patients.

a) Problems with the APEX trial

The decision to include the APEX trial initially was well justified because it was and remains the only trial that has compared LMWH to a DOAC for VTE prophylaxis in cancer patients. Unfortunately, the APEX study, which was the only trial addressing whether DOACs were acceptable alternatives to LMWHs that utilized betrixaban, had a trial population that was acutely ill with a number of confounding medical conditions associated with a high degree of mortality. The degree to which other very active disease states play a role in VTE genesis would need to be considered had this trial shown a statistical advantage of the factor Xa inhibitor over the LMWH. As noted previously, the APEX trial did not have ultrasound follow-up in 15% of enrolled patients, thus could not include more than 1 in 7 patients in the main efficacy analysis. Therefore, further confounding any possible clinical applicability of the results. The study was also troubled by the fact that it failed to demonstrate a benefit of betrixaban over enoxaparin with regard to efficacy, though rates of both interventions were lower than we would have expected (6.7-12.9%) had the intervention been placebo.(32) Therefore, one could surmise that both interventions would

be of potential benefit in cancer patients without cerebral neoplasms or metastases as well as in those with lung cancer who were also excluded by design. The fatal flaw, with respect to any interpretation for cancer patients was the fact that most patients in the cancer subgroup were actually individuals with a history of cancer and not those with active neoplasms and outcomes were not separated by this critical distinction. This factor alone makes any interpretation with regard to patients with active cancer almost meaningless. Thus, any clinical guidance gleaned from other evidence regarding betrixaban could only be included as part of a class-effect as well and not from direct clinical trail data. It is for this reason that further discussion shall focus on the other three trials, as any design, protocol or interpretation critique becomes moot when considering that this study cannot be generally considered as having adequately isolated our target population and even if that assumption were granted, we are also uncertain as to types and frequency of cancers that were included.

b) Dabigatran, Edoxaban, and Betrixaban

Of the trials looking at VTE prophylaxis in patients with cancer, none involved the direct thrombin inhibitor dabigatran or the factor Xa inhibitor edoxaban. Thus, any conclusions gleaned from the data would be pure conjecture with regard to the mechanistically unique dabigatran and would have to be presumed based upon class effect when considering edoxaban. This is a commonly made assumption, but can be misleading, especially when considering that edoxaban has the highest degree of renal clearance of all factor Xa inhibitors.(35) Keeping in mind that we have already excluded the betrixaban APEX trial due to uncertainty regarding the true clinical status of the cancer subgroup, we are left with trials and data concerning only two direct oral anticoagulants, namely apixaban and rivaroxaban.

c) Cancer sub-types: Cui bono?

The Levine and CASSINI trails excluded patients with brain neoplasms or metastases as well, whereas AVERT included such patients. AVERT and Levine had a small number of myeloma patients, whereas these were excluded in CASSINI. Apart from AVERT disclosing that 80% of major bleeding events occurred in GI or gynecologic malignancies, none of the aforementioned studies broke down event rates by cancer sub-type. Due to the varied types of cancer in all three studies and low overall event rates, it is uncertain if any statistically significant data could have been derived from those added data. It would most likely be unfeasible to have large trials looking at large cohorts of specific cancer types, but because of the relatively small number of patients involved when breaking down the studies into disease subtypes, it is unclear whether other cancers are associated with higher or lower efficacy and safety outcome event rates than others. Therefore, it would appear to require subspecialty expertise in discerning applicability of such data.

With the exclusion of the acutely ill patients in the APEX trial due to aforementioned reasons, we are able to make a few very sweeping generalizations with regard to which cancer patients these data could be applicable to. The remaining trials involved only ambulatory cancer patients with relatively intact renal function (CrCl > 30 ml/min) and no active bleeding diatheses. The two large trials (AVERT and CASSINI) also only included patients with validated risk assessment scores that placed those patients at intermediate to high risk of VTE events. This understandably limits applicability of any findings to within these criteria, but these criteria are defensible on the grounds that the researchers were attempting to establish a group that could maximally benefit from intervention all the while being cognisant of safety implications. It is notable that brain metastases, which were only non-exclusory in the AVERT trail, did not appear to effect outcomes one way or another, but no definitive conclusions can be drawn due to this being only a small subset of a singular

trial. Conversely, as mentioned previously the AVERT trial did provide some insight into the sorts of malignancies at greatest risk of adverse effects, with the vast majority (80%) of major bleeds in that trial taking place in those with gynecologic of primary GI malignancies. This is in keeping with results from other trials looking at bleeding when treating rather than preventing cancer related VTEs with DOACs.(36,37) Thus, it may be reasonable to conduct a larger scale DOAC trail that excludes those cancer subtypes and one might conjecture that major bleeding may decrease proportionately.

d) Endpoint Analysis

The primary safety and efficacy endpoints were well defined and in line with major trials looking at thromboprophylaxis with various types of anticoagulants.(32) The utilization of placebo control within these trials was justified on the grounds that there is no current recommended intervention for thromboprophylaxis in this context among this specific population. (8) Even though efficacy has also been shown in trials involving LMWH, relatively large NNT of over 50 and uncertain NNH preclude a general recommendation of ambulatory cancer patient thromboprophylaxis. (7,8,38) These trials were therefore designed similarly to previous trials involving LWMH, uLMWH, and warfarin; thus, they allow the clinician to compare safety and efficacy data across trials to an extent greater than comparisons of other parameters.

The Levine trial demonstrated an initial efficacy advantage among the selected population for VTE prevention and apart from the 20 mg dose, the 5 mg and 10 mg dosage appeared to not be associated with any major bleeding. This was a promising result but required CASSINI and AVERT to be conducted on larger populations and for longer durations to have a better idea as to the efficacy and safety profile of apixaban and rivaroxaban. Despite targeting high risk groups in both AVERT and CASSINI, only AVERT was able to demonstrate a confidence interval that was statistically significant in terms of

efficacy but AVERT also had the dubious distinction of having a significant interval, albeit only just, with regard to major bleeding. A confounding factor with regard to the results achieved in AVERT is that distal DVT was not included as a primary outcome as it had been in the other analyzed trials. This may have attenuated the VTE outcome and could partially explain the 2% absolute discrepancy between VTEs experienced in the large rivaroxaban and apixaban trials.

CASSINI was not able to cross the threshold of statistical significance for efficacy or bleeding rates during the 180-day protocol but was able to demonstrate a statistically significant advantage for rivaroxaban when analyzing only the intervention period. Though the remaining results were not at the threshold of significance, efficacy and safety did follow the expected result of DOAC superiority to placebo with regard to efficacy and placebo associated with less bleeding. This being noted, bleeding rates were similar (around 1%) in AVERT and CASSINI compared to studies looking at LMWH, but absolute VTE risk reduction occurred in closer to 5% of patients versus an average of 2.5% in LMWH studies. (8) This is most likely attributable to AVERT and CASSINI utilizing higher risk patients based on Khorana score, rather than some underlying characteristic of the drugs. As clinical trials comparing DOACs to LMWH in terms of efficacy in treatment of VTE, rather than prophylaxis, do not demonstrate this magnitude of disparate absolute risk reduction.(39)

e) Study Completion Rates

Discontinuation rates among patients in the trials ranged from a low of 22% in the Levine trial to a high of 47% in the CASSINI trial and with AVERT in between at 30%. The three-month duration of the Levine trial versus six months of CASSINI and AVERT probably account for why Levine had the lowest rate, whereas, as previously mentioned, CASSINI and AVERT had disparate cancer populations but the rates of discontinuation and reasons for doing so are in keeping with similar studies looking at LMWH vs placebo in

similar populations. (7,38) The reasons provided for discontinuation in the studies supplementary appendices were varied and did not appear too significant in the sense that the conclusions drawn from the outcomes were biased in one direction or another. However, at least with regard to the CASSINI trial, the huge proportion of trial discontinuation appears to have ensured that no statistical benefit toward rivaroxaban could be shown. This notion is supported by the fact that the efficacy during the intervention period only did indicate a benefit. Unfortunately, this begs the question as to whether the non-significant difference in bleeding rates could also be attributed to this rate of premature termination.

f) Clinical Practice Implications

Due to the paucity of data exploring DOAC usage for VTE prophylaxis in cancer patients, guidelines have yet to incorporate strong recommendations regarding their use in this population.(11) New conditional recommendations with regard to apixaban or rivaroxaban use in patients deemed to be at intermediate to high risk based on validated risk assessment scores are clearly attributable to the evidence provided by the AVERT and CASSINI trials that followed preliminary data gathered by Levine in 2012.

The AVERT trial did provide some evidence to complement information gleaned from the Hokusai-VTE and Select-D trails that had both studied treatment of VTE in cancer patients with edoxaban and rivaroxaban respectively against the current treatment standard of LMWH (specifically dalteparin).(36,37) The majority of major bleeding in patients from DOACs in all three trials clustered around patients with gynecologic or GI related cancers. Although no studies have specifically looked at bleeding in just this population, this is hypothesis generating at least with regard to specific populations more at risk of complications with DOAC use.

There were no other patient characteristics that stood out from these studies in a way that was suggestive that further research should be conducted to see if DOACs should be considered as contraindicated or of particular benefit. This being stated, only AVERT did not exclude patients with primary cerebral neoplasms or brain metastases. Thus, although subgroup analysis did not demonstrate a specific concern in this population, considering how few individuals this represents, no definitive statement can be made regarding DOAC use for VTE prevention in this population.

It is unfortunate that the APEX trial, which compared the LMWH enoxaparin to betrixaban, had so many confounding medical conditions, exclusion criteria and poor data collection because this is the only trial that has ever studied prevention of cancer related VTE and compared LMWH to a DOAC, even if only as a sub-population. There is clearly a need for further research comparing DOACs and LMWHs head-to-head for prevention of cancer related VTE, as this would hopefully clarify and allow guidelines to provide stronger and clearer recommendations related to when and for whom to use each. Realistically, there have only been AVERT and CASSINI that have demonstrated modest benefit for preventing cancer related VTEs in intermediate to high-risk patients. Studies that could compare both conditionally recommended medication classes in this population would allow clinicians to have more data to discern the magnitude of efficacy and risk as well as lead to future stronger recommendations for use in general and preliminary suggestions of one treatment class over another.

Although it has previously been mentioned, it bears repeating that we are well aware of theoretical drug-drug interactions of DOACs due to their known metabolism by CYP3A4 and susceptibility to cell efflux by P-glycoproteins. It is known that greater than 50% of available chemotherapeutic agents and other clinically used drugs are effected by these mechanisms.(40) Though there are general precautions advising caution and consideration for

alternate combinations with known strong inhibitors and inducers of P-glycoprotein and CYP3A4, specific direction pertaining to commonly utilized chemotherapeutic drugs has yet to materialize.(41) After a decade of increased clinical use, this is reassuring. However, with the relative novelty of these agents being combined with cancer drugs there remains the risk that contraindicated combinations may yet emerge.

Given that the absolute risk reductions and risk increases were either modest and or not statistically significant in the analyzed trials, further research comparing DOACs to LMWHs in these populations may only be helpful in further clarifying whether a significant enough benefit is achieved in intermediate to high-risk patients to justify stronger recommendations. This research may also expand the list of DOACs that could be recommended from only rivaroxaban and apixaban as well as begin to provide some guidance as to whether DOACs could specifically be singled out as the intervention of choice over LMWHs.

Though it made sense to compare DOACs to placebo due to no treatment previously being recommended for VTE prophylaxis prior to recent guidelines being published, it is unlikely that future studies will be approved to look at DOACs vs LMWHs in lower risk cancer cohorts. The reality is that both CASSINI and AVERT were only able to demonstrate modest benefit to intermediate to high-risk sub-populations and prior LMWH prophylaxis trials had only demonstrated modest benefit to high-risk groups, unclear benefit to intermediate risk groups and limited to no benefit in lower risk populations.(11) Thus, the need to explore DOAC use in lower risk cohorts appears dubious at best. It is also important to recall that although DOACs do not necessitate ongoing blood monitoring, they are not free nor inexpensive, and can lead to a significant financial burden for patients or third-party payers. As a consequence, even modest benefits need to be weighed against very real financial constraints and recommendations stemming from future trial data should consider this prior to making sweeping changes to the current standards of practice.

Limitations

This review was limited by the few RCTs that have been published assessing VTE prophylaxis with DOACs in cancer patients and the fact that apart from the APEX trial, which only had a subpopulation of patients with a cancer history, none have directly compared DOACs to LMWHs in this population. A separate factor to be considered is that the studies that were included in this review did not include consistent populations, making direct comparisons between trials difficult. The trials that exist also did not look at thromboprophylaxis in cancer patients about to undergo surgery. Nor did any trials address DOAC usage in medically ill inpatients with cancer without VTE, apart from the previously maligned APEX trial. Thus, any conclusions regarding DOAC usage in surgical cancer patients and medically ill inpatients could not be evidence based and have rightfully not been included in recent guidelines. Finally, it is imperative to remember that any conclusions hoping to be drawn from peer-reviewed evidence must at present be limited to apixaban and rivaroxaban, as the other DOACs have not been included in any scientific trials in this target population.

Conclusion

VTE continues to be a major concern for cancer patients and a significant cause of morbidity and mortality in such individuals. Unfortunately, the evidence available to date is unconvincing with respect to the benefits that DOACs (apixaban and rivaroxaban specifically) provide in the prevention of VTE in cancer, apart from modest benefits in selected high-risk individuals. For such individuals, it appears as though apixaban and rivaroxaban may be of some benefit, but further research is necessary to make such a recommendation unequivocal. We can, however, likely assert that when validated risk assessment scores identify intermediate to high-risk individuals with relatively intact renal

function with most cancer subtypes, that apixaban or rivaroxaban are probably equally as valid prophylactic options as LMWHs. This assertion is not so much a glowing endorsement of intervention, rather an indictment of the evidence available regarding LMWH use in prophylaxis. What is undeniably necessary is further research comparing LMWHs and DOACs head-to-head in intermediate to high-risk populations. Such research would hopefully expand on the pool of available DOACs for consideration, and further clarify the extent of benefit for either intervention as well as potentially point toward the superiority or non-inferiority of DOACs for such patients.

Neither LMWH nor DOAC trails have specifically established that GI or gynecologic malignancies are cancer subtypes that should avoid LMWH or DOAC use due to a higher risk of major bleeding. However, AVERT has added to a body of evidence from LMWH trials showing that major bleeding tends to be more prevalent with anticoagulation attempts in this population. This theme requires further exploration by appropriate trial design and subgroup analysis in future research such as that which was posited in the preceding paragraph.

Appendix

Recommendations taken from American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer (11)

Primary prophylaxis for hospitalized medical patients with cancer.

Recommendation 1.

For hospitalized medical patients with cancer without VTE, the American Society of Hematology (ASH) guideline panel *suggests* using thromboprophylaxis over no thromboprophylaxis (conditional recommendation, very low certainty in the evidence of effects).

Recommendation 2.

For hospitalized medical patients with cancer without VTE, in which pharmacological thromboprophylaxis is used, the ASH guideline panel *suggests* using LMWH over UFH (conditional recommendation, low certainty in the evidence of effects).

Recommendation 3.

For hospitalized medical patients with cancer without VTE, the ASH guideline panel *suggests* using pharmacological thromboprophylaxis over mechanical thromboprophylaxis (conditional recommendation, very low certainty in the evidence of effects).

Recommendation 4.

For hospitalized medical patients with cancer without VTE, the ASH guideline panel *suggests* using pharmacological thromboprophylaxis over a combination of pharmacological and mechanical thromboprophylaxis (conditional recommendation, very low certainty in the evidence of effects).

Recommendation 5.

For hospitalized medical patients with cancer, the ASH guideline panel *suggests* discontinuing thromboprophylaxis at the time of hospital discharge rather than continuing thromboprophylaxis beyond the discharge date (conditional recommendation, very low certainty in the evidence of effects).

Primary prophylaxis for patients with cancer undergoing surgery.

Recommendation 6.

For patients with cancer without VTE undergoing a surgical procedure at lower bleeding risk, the ASH guideline panel *suggests* using pharmacological rather than mechanical thromboprophylaxis (conditional recommendation, low certainty in the evidence of effects).

Recommendation 7.

For patients with cancer without VTE undergoing a surgical procedure at high bleeding risk, the ASH guideline panel *suggests* using mechanical rather than pharmacological thromboprophylaxis (conditional recommendation, low certainty in the evidence of effects).

Recommendation 8.

For patients with cancer without VTE undergoing a surgical procedure at high risk for thrombosis, except in those at high risk of bleeding, the ASH guideline panel *suggests* using a combination of mechanical and pharmacologic thromboprophylaxis rather than mechanical

prophylaxis alone (conditional recommendation based on low certainty in the evidence of effects) or pharmacologic thromboprophylaxis alone (conditional recommendation, very low certainty in the evidence of effects).

Recommendation 9.

For patients with cancer undergoing a surgical procedure, the ASH guideline panel *suggests* using LMWH or fondaparinux for thromboprophylaxis rather than UFH (conditional recommendation, low certainty in the evidence of effects).

Recommendation 10.

For patients with cancer undergoing a surgical procedure, the ASH guideline panel makes no recommendation on the use of VKA or DOAC for thromboprophylaxis, because there were no studies available.

Recommendation 11.

For patients with cancer undergoing a surgical procedure, the ASH guideline panel *suggests* using postoperative thromboprophylaxis over preoperative thromboprophylaxis (conditional recommendation, low certainty in the evidence of effects).

Recommendation 12.

For patients with cancer who had undergone a major abdominal/pelvic surgical procedure, the ASH guideline panel *suggests* continuing pharmacological thromboprophylaxis post discharge rather than discontinuing at the time of hospital discharge (conditional recommendation, very low certainty in the evidence of effects).

Primary prophylaxis in ambulatory patients with cancer receiving systemic therapy.

Recommendation 13.

For ambulatory patients with cancer at low risk for thrombosis receiving systemic therapy, we *recommend* no thromboprophylaxis over parenteral thromboprophylaxis (strong recommendation, moderate certainty in the evidence of effects).

For ambulatory patients with cancer at intermediate risk for thrombosis receiving systemic therapy, the ASH guideline panel *suggests* no prophylaxis over parenteral prophylaxis (conditional recommendation, moderate certainty in the evidence of effects).

For ambulatory patients with cancer at high risk for thrombosis receiving systemic therapy, the ASH guideline panel *suggests* parenteral thromboprophylaxis (LMWH) over no

thromboprophylaxis (conditional recommendation, moderate certainty in the evidence of effects).

Recommendation 14.

For ambulatory patients with cancer receiving systemic therapy, the ASH guideline panel *recommends* no thromboprophylaxis over oral thromboprophylaxis with VKA (strong recommendation, very low certainty in the evidence of benefits, but high certainty about the harms).

Recommendation 15.

For ambulatory patients with cancer at low risk for thrombosis receiving systemic therapy, the ASH guideline panel *suggests* no thromboprophylaxis over oral thromboprophylaxis with a DOAC (apixaban or rivaroxaban) (conditional recommendation, moderate certainty in the evidence of effects).

For ambulatory patients with cancer at intermediate risk for thrombosis receiving systemic therapy, the ASH guideline panel *suggests* thromboprophylaxis with a DOAC (apixaban or rivaroxaban) or no thromboprophylaxis (conditional recommendation, moderate certainty in the evidence of effects).

For ambulatory patients with cancer at high risk for thrombosis receiving systemic therapy, the ASH guideline panel *suggests* thromboprophylaxis with a DOAC (apixaban or rivaroxaban) over no thromboprophylaxis (conditional recommendation, moderate certainty in the evidence of effects).

Recommendations 16 and 17.

For multiple myeloma patients receiving lenalidomide, thalidomide, or pomalidomide-based regimens, the ASH guideline panel *suggests* using low-dose acetylsalicylic acid (ASA) or fixed low-dose VKA or LMWH (conditional recommendation, low certainty in the evidence of effects).

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