original article

Prophylaxis and treatment of venous thromboembolism in patients with cancer: the Saudi clinical practice guideline

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BACKGROUND AND OBJECTIVES: Venous thromboembolism (VTE) is commonly encountered in the daily clinical practice. Cancer is an important VTE risk factor. Proper thromboprophylaxis is key to prevent VTE in patients with cancer, and proper treatment is essential to reduce VTE complications and adverse events associated with the therapy.

DESIGN AND SETTINGS: As a result of an initiative of the Ministry of Health of Saudi Arabia, an expert panel led by the Saudi Association for Venous Thrombo-Embolism (a subsidiary of the Saudi Thoracic Society) and the Saudi Scientific Hematology Society with the methodological support of the McMaster University working group produced this clinical practice guideline to assist health care providers in evidence-based clinical decision-making for VTE prophylaxis and treatment in patients with cancer.

METHODS: Six questions related to thromboprophylaxis and antithrombotic therapy were identified and the corresponding recommendations were made following the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach.

RESULTS:

Question 1. Should heparin versus no heparin be used in outpatients with cancer who have no other therapeutic or prophylactic indication for anticoagulation?

Recommendation: For outpatients with cancer, the Saudi Expert Panel suggests against routine thromboprophylaxis with heparin (weak recommendation; moderate quality evidence).

Question 2. Should oral anticoagulation versus no oral anticoagulation be used in outpatients with cancer who have no other therapeutic or prophylactic indication for anticoagulation?

Recommendation: For outpatients with cancer, the Saudi Expert Panel recommends against thromboprophylaxis with oral anticoagulation (strong recommendation; moderate quality evidence).

Question 3. Should parenteral anticoagulation versus no anticoagulation be used in patients with cancer and central venous catheters?

Recommendation: For outpatients with cancer and central venous catheters, the Saudi Expert Panel suggests thromboprophylaxis with parenteral anticoagulation (weak recommendation; moderate quality evidence).

Question 4. Should oral anticoagulation versus no anticoagulation be used in patients with cancer and central venous catheters?

Recommendation: For outpatients with cancer and central venous catheters, the Saudi Expert Panel suggests against thromboprophylaxis with oral anticoagulation (weak recommendation; low quality evidence).

Question 5. Should low-molecular-weight heparin versus unfractionated heparin be used in patients with cancer

being initiated on treatment for venous thromboembolism?

Recommendation: In patients with cancer being initiated on treatment for venous thromboembolism, the Saudi Expert Panel suggests low-molecular-weight heparin over intravenous unfractionated heparin (weak; very low quality evidence).

Question 6. Should heparin versus oral anticoagulation be used in patients with cancer requiring long-term treatment of VTE?

Recommendation: In patients with metastatic cancer requiring long-term treatment of VTE, the Saudi Expert Panel recommends low-molecular-weight heparin (LMWH) over vitamin K antagonists (VKAs) (strong recommendation; moderate quality evidence). In patients with non-metastatic cancer requiring long-term treatment of venous thromboembolism, the Saudi Expert Panel suggests LMWH over VKA (weak recommendation; moderate quality evidence).

Venous thromboembolism (VTE), comprising deep venous thrombosis (DVT) and pulmonary embolism, is a relatively common disease with cancer being one of its important risk factors.[1] In fact, patients with cancer have an approximately sevenfold increased risk of VTE compared with those without cancer.[2] The malignant cells themselves induce a hypercoagulable state,[3] and the cancer type, stage, and histological grade contribute to the thrombosis risk.[4] Additionally, factors related to cancer management, such as surgery, chemotherapy, radiotherapy, hormonal therapy, hospitalization, and indwelling central venous catheters, increase further the VTE risk.[5] Prophylaxis and treatment of VTE can be challenging, as patients with cancer have a higher risk of both VTE recurrence and bleeding complications.[6] Hence, the proper selection of VTE prophylaxis and treatment modalities and their use in the right setting is crucial.

According to the Saudi Cancer Registry, cancer incidence in Saudi Arabia in 2010 was 13 706 patients.[7] Based on data from the Middle East, it is estimated that the 5-year cancer prevalence is 0.28% of the population, which corresponds to approximately 80 000 patients in Saudi Arabia.[8] Clinical data from Saudi Arabia on VTE in cancer patients are scarce. A retrospective study of 701 patients with solid tumors or lymphoma who were treated at a tertiary-care center in Riyadh from 2004 to 2009 found that VTE was diagnosed in 6.7% with 79% of VTE patients having an advanced cancer stage.[9]

Aiming at guiding health care providers working in Saudi Arabia in evidence-based VTE management, the Saudi Ministry of Health (MoH) arranged for this clinical practice guideline and obtained the methodological support of the McMaster University guidelines group. In this document, we report the recommendations of the Saudi expert panel for VTE prophylaxis and treatment in cancer patients.

METHODS

In 2013, the Saudi MoH embarked on a program of rigorous adaptation and de novo development of clinical practice guidelines to provide guidance for clinicians to ensure high quality of care and reduce variability in clinical practice across Saudi Arabia. Hence, the Saudi MoH, through the Saudi Center for Evidence-Based Healthcare, partnered with the McMaster University guidelines group to provide methodological support and contacted the Saudi Scientific Hematology Society and the Saudi Association for VTE to nominate a group of clinicians to serve as an expert panel for guideline development on VTE prophylaxis and treatment in cancer patients. In the following, we briefly describe the methodology used to develop recommendations and grade the quality of the supporting evidence. The details of the methodology are available in a separate publication.[10]

The overall process

The Saudi Arabia guideline panel selected the topic of this guideline and all related questions using a formal prioritization process. For all selected questions, the McMaster University working group identified the related systematic reviews of randomized controlled trials published in the Cochrane Library, and then searched for trials that were subsequently published in Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE until November 2013. The reviews were then updated by incorporating the new eligible trials. These updates were later published in the Cochrane Library.[11-16] The group also conducted systematic searches for information that was required to develop full guidelines for Saudi Arabia, including searches for information about patients' values and preferences and cost (resource use) specific to the Saudi context.

Next, the McMaster guideline leader developed for each question a summary of findings table and an evi-

dence-to-recommendation table and shared them with the panel members. The guideline panel was invited to provide additional information, particularly when published evidence was lacking. The final step consisted of an in-person meeting of the guideline panel in Riyadh on December 3, 2013, to develop the final recommendations. We used the evidence-to-recommendation tables to follow the structured consensus process and transparently document all decisions made during the meeting. The guideline panel formulated all recommendations during this meeting. Potential conflicts of interests of all panel members were managed according to the World Health Organization rules.[17]

The selected questions

The following is a list of the clinical questions selected by the Saudi Arabia guideline panel and addressed in this guideline. For details on the process by which the questions were selected, please refer to the separate methodology publication.[10]

1. Should heparin versus no heparin be used in outpatients with cancer who have no other therapeutic or prophylactic indication for anticoagulation?
2. Should oral anticoagulation versus no oral anticoagulation be used in outpatients with cancer who have no other therapeutic or prophylactic indication for anticoagulation?
3. Should parenteral anticoagulation versus no anticoagulation be used in patients with cancer and central venous catheters?
4. Should oral anticoagulation versus no anticoagulation be used in patients with cancer and central venous catheters?
5. Should low-molecular-weight heparin (LMWH) versus unfractionated heparin (UFH) be used in patients with cancer being initiated on treatment for venous thromboembolism?
6. Should heparin versus oral anticoagulation be used in patients with cancer requiring a long-term treatment of VTE?

Grading the quality of evidence

The panel assessed the quality of evidence using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach.[18] Quality of evidence was classified as "high," "moderate," "low," or "very low" based on decisions about methodological characteristics of the available evidence for a specific health care problem. The definition of each category is as follows:[19]

* High: We are very confident that the true effect lies close to that of the estimate of the effect.
* Moderate: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
* Low: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
* Very low: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Grading the strength of recommendations

The GRADE Working Group defines the strength of recommendation as the extent to which we can be confident that desirable effects of an intervention outweigh undesirable effects.[20] According to the GRADE approach, the strength of a recommendation is either strong or conditional (weak) and has explicit implications (**Table 1**).[20] Understanding the interpretation of these 2 grades—either strong or conditional—of the strength of recommendations is essential for sagacious clinical decision-making.

The panel provided recommendations to cover the following 2 major topics: (1) Thrombo-prophylaxis in patients with cancer (Questions 1-4) and (2) Antithrombotic therapy in patients with cancer (Questions 5-6). The recommendations were made taking into consideration the available evidence, resource used, and the Saudi context.

RESULTS

The evidence for this guideline was based on 5 systematic reviews and meta-analysis,[21-25] which included 51 eligible trials. The inclusion and exclusion criteria are detailed in the reviews.[21-25] The updated search found 6 trials that were included in the updated meta-analyses. The full guideline with details of published report grading and recommendation process is available at: *http://www.moh.gov.sa/depts/Proofs/Pages/Guidelines.aspx*.

I. Thromboprophylaxis in patients with cancer

Question 1: Should heparin versus no heparin be used in outpatients with cancer who have no other therapeutic or prophylactic indication for anticoagulation?

The summary of evidence is based on a Cochrane systematic review by Akl et al.[21] The updated published report search identified 3 additional studies that were included in the meta-analyses.[26-28] Subgroup analyses by the type or stage of cancer were either not feasible or inconclusive. The summary of findings is reported in **Table 2**.[21,26-28]

Benefits of the option: The meta-analysis of 13 studies (7266 participants) found the moderate quality evidence for reduction in mortality (RR 0.95; 95% CI 0.89 to 1.00; absolute effect: 23 fewer per 1000 over 1 year).[21] The meta-analysis had some but no serious heterogeneity across studies (I^2=15%).[21] The meta-analysis of 12 studies (6998 participants) found the high quality evidence for reduction in VTE (RR 0.65; 95% CI 0.43 to 0.74; absolute effect: 23 fewer per 1000 over 1 year).[21]

Harms of the option: The meta-analysis of 14 studies (7539 participants) found the moderate quality evidence of increase in major bleeding (RR 1.14; 95% CI 0.80 to 1.63; absolute effect: 2 more per 1000).[21] The meta-analysis of 12 studies (7041 participants) found the moderate quality evidence of increase in minor bleeding (RR 1.32; 95% CI 1.03 to 1.70; absolute effect: 9 more per 1000).[21]

Values and preferences: The panel's judgment was that the typical patient would be against daily injections for duration of several months. Patients would view a potential reduction in mortality and symptomatic VTE favorably.

Resource use: The panel estimated the daily cost of an LMWH to be low. For example, the daily cost of enoxaparin was estimated at SR 20 per injection, a small unit cost. Applying this to the population level for a period of 6 months results in estimated costs of SR 36 million per 10 000 cancer patients. Considering that a certain number of patients would not do self-injection (maybe as high as 50% of patients), they would have to go to a clinic or have nurse home visits.

Other considerations: The panel judgment was that it would be hard for policymakers to accept the intervention due to the cost and given this is a prophylaxis intervention.

Recommendation 1:
For outpatients with cancer, the Saudi Expert Panel suggests against routine thromboprophylaxis with

Table 1. Interpretation of strong and conditional (weak) recommendations.

Implications	Strong recommendation	Conditional (weak) recommendation
For patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful helping individuals making decisions consistent with their values and preferences.
For policy makers	The recommendation can be adapted as policy in most situations	Policy making will require substantial debate and involvement of various stakeholders.

Table 2. Summary of findings: Heparin versus no heparin be used in patients with cancer who have no other therapeutic or prophylactic indication for anticoagulation.

Patient or population: Patients with cancer who have no other therapeutic or prophylactic indication for anticoagulation Intervention: LMWH Comparison: No LMWH					
Outcomes	Illustrative comparative risks[a] (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk No LMWH	Corresponding risk LMWH			
Mortality at 12 mo Follow-up: 12 mo	459 per 1000	436 per 1000 (409–459)	RR 0.95 (0.89–1)	7266 (13 studies)	Moderate
Symptomatic VTE	51 per 1000	29 per 1000 (22–38)	RR 0.56 (0.43–0.74)	6998 (12 studies)	High
Major bleeding	16 per 1000	18 per 1000 (13–26)	RR 1.14 (0.8–1.63)	7539 (14 studies)	Moderate
Minor bleeding	28 per 1000	31 per 1000 (25–44)	RR 1.1 (0.89–1.55)	7041 (12 studies)	High

CI, Confidence interval; LMWH, low molecular weight heparin; RR, risk ratio; VTE, venous thromboembolism; GRADE, Grading of Recommendations, Assessment, Development and Evaluation.

[a]The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

heparin. (weak recommendation; moderate quality evidence)

Remarks:

* Use a validated tool (e.g., the Khorana risk assessment score[29]) to risk stratify patients, as those at a higher risk for VTE are more likely to benefit
* This recommendation does not apply to patients who would otherwise have an indication for prophylaxis. Examples include: immobility, long-distance travel, highly thrombogenic drugs (e.g., thalidomide, lenalidomide, hormonal therapy, angiogenesis inhibitors), and high-risk cancer surgery patients.
* See separate recommendation for oral anticoagulation

Subgroup considerations: Although there is evidence for potential benefit in patients with small cell lung cancer, the evidence is of lower quality, so the recommendation applies to all types of cancers.

Question 2: Should oral anticoagulation versus no oral anticoagulation be used in outpatients with cancer who have no other therapeutic or prophylactic indication for anticoagulation?

The summary of evidence (**Table 3**) is based on a Cochrane systematic review by Akl et al.[22] The updated published report search identified 1 additional phase II trial comparing apixaban to placebo.[30] The trial included patients with cancer receiving chemotherapy and who were at an increased risk for thrombosis.[30] Including the study in the meta-analyses did not substantively affect the results.

Benefits of the option: The meta-analysis of 5 studies (1604 participants) found moderate quality evidence of no effect on mortality (RR 0.94; 95% CI 0.87 to 1.03; absolute effect: 39 fewer per 1000 over 1 year).22 One study (315 participants) found the moderate quality evidence for reduction in VTE (RR 0.15; 95% CI 0.02 to 1.2; absolute effect: 25 fewer per 1000 over 1 year).[22]

Harms of the option: The meta-analysis of 4 studies (1282 participants) found moderate quality evidence of increase in major bleeding (RR 4.24; 95% CI 1.85 to 9.68; absolute effect: 23 more per 1000).[22] The meta-analysis of 3 studies (851 participants) found moderate quality evidence of increase in minor bleeding (RR 3.34; 95% CI 1.66 to 6.74; absolute effect: 63 more per 1000).[22]

Values and preferences: The panel thought that the typical patient would find oral anticoagulation burdensome due to the frequent testing and monitoring, diet and medication restrictions, stoppage for procedures,

Table 3. Summary of findings: Oral anticoagulation versus no oral anticoagulation be used in patients with cancer who have no other therapeutic or prophylactic indication for anticoagulation.

Patient or population: Patients with cancer who have no therapeutic or prophylactic indication for anticoagulation Settings: Outpatient Intervention: Oral anticoagulation[a]					
Outcomes	Illustrative comparative risks[b] (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Control	Corresponding risk Oral anticoagulation			
Death Follow-up: median 1 y	Moderate 649 per 1000	610 per 1000 (565–668)	RR 0.94 (0.87–1.03)	1604 (5 studies)	Moderate
Symptomatic VTE Follow-up: 1 y	Moderate 29 per 1000	4 per 1000 (1–35)	RR 0.15 (0.02–1.2)	315 (1 study)	Moderate
Major bleeding Follow-up: median 1 y	Moderate 7 per 1000	30 per 1000 (13–68)	RR 4.24 (1.85–9.68)	1282 (4 studies)	Moderate
Minor bleeding Follow-up: 1 y	Moderate 27 per 1000	90 per 1000 (45–182)	RR 3.34 (1.66–6.74)	851 (3 studies)	Moderate

CI, Confidence interval; INR, international normalized ratio; RR, risk ratio; VTE, venous thromboembolism; GRADE, Grading of Recommendations, Assessment, Development and Evaluation.

[a]All studies used warfarin at a dose to increase prothrombin time 1.5 to 2 times (4 studies) or to keep INR between 1.3 and 1.9.

[b]The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

etc. Patients would view a potential reduction in mortality and symptomatic VTE favorably.

Resource use: The panel estimated the unit cost to be low. However, visits for monitoring and lab testing would require significant resources.

Other considerations: While the panel thought the intervention would be feasible, they judged it as probably not acceptable because of the lack of effectiveness (no effect on mortality) and cost-effectiveness.

Recommendation 2:
For outpatients with cancer, the Saudi Expert Panel recommends against thromboprophylaxis with oral anticoagulation. (strong recommendation; moderate quality evidence).

Key consideration:

* This recommendation does not apply to patients who would otherwise have an indication for prophylaxis. Examples include: immobility, long-distance travel, highly thrombogenic drugs (e.g., thalidomide, lenalidomide, hormonal therapy, angiogenesis inhibitors).
* See separate recommendation for heparin anticoagulation.

Table 4a. Summary of findings: Parenteral anticoagulation versus no parenteral anticoagulation be used in cancer patients with central venous catheters.

Patient or population: Patients with thrombosis prophylaxis in cancer patients with central venous catheters Settings: Outpatient or inpatient Intervention: Heparin Comparison: No heparin					
Outcomes	Illustrative comparative risks[a] (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk No heparin	Corresponding risk Heparin			
Death	64 per 1000	54 per 1000 (35–83)	RR 0.85 (0.55–1.31)	1474 (6 studies)	Moderate
Symptomatic DVT	80 per 1000	43 per 1000 (28–68)	RR 0.54 (0.35–0.85)	1455 (7 studies)	High
Major bleeding	5 per 1000	4 per 1000 (1–26)	RR 0.68 (0.1–4.78)	891 (4 studies)	Moderate
Infection	71 per 1000	65 per 1000 (35–120)	RR 0.91 (0.49–1.68)	626 (3 studies)	Moderate
Thrombocytopenia	156 per 1000	163 per 1000 (125–210)	RR 1.04 (0.8–1.34)	1118 (4 studies)	Moderate

CI, Confidence interval; RR, risk ratio; DVT, deep vein thrombosis; GRADE, Grading of Recommendations, Assessment, Development and Evaluation..

[a]The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Table 4b. Summary of findings: Parenteral anticoagulation versus oral anticoagulation be used in cancer patients with central venous catheters.

Patient or population: Patients with thrombosis prophylaxis in cancer patients with central venous catheters Settings: Outpatient or inpatient Intervention: LMWH Comparison: VKA					
Outcomes	Illustrative comparative risks[a] (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk VKA	Corresponding risk LMWH			
Death	87 per 1000	96 per 1000 (56—168)	RR 1.11 (0.64–1.93)	623 (3 studies)	Low
Symptomatic DVT	43 per 1000	67 per 1000 (33–137)	RR 1.55 (0.76–3.15)	560 (3 studies)	Low
Major bleeding	0 per 1000	0 per 1000 (0–0)	RR 3.1 (0.13–73.14)	343 (2 studies)	Low
Thrombocytopenia	202 per 1000	346 per 1000 (245–492)	RR 1.71 (1.21–2.43)	339 (2 studies)	Moderate

CI, Confidence interval; DVT, deep vein thrombosis; LMWH, low molecular weight heparin; RR, Risk ratio; VKA, vitamin K antagonist.

[a]The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Question 3: Should parenteral anticoagulation versus no anticoagulation be used in patients with cancer and central venous catheters?

The summary of evidence (**Tables 4a & b**) is based on a systematic review by Akl et al.[23] The updated published report search identified 1 new trial that randomized patients with planned chemotherapy for cancer to no anticoagulant prophylaxis, LMWH, or warfarin 1 mg/d.[31]

Benefits of the option: The meta-analysis of 6 studies (1474 participants) found moderate quality evidence that did not rule out either an increase or a decrease in mortality (RR 0.85; 95% CI 0.55 to 1.31; absolute effect: 10 fewer per 1000 over 1 year).[23] The meta-analysis of 7 studies (1455 participants) found the high quality evidence for reduction in VTE (RR 0.54; 95% CI 0.35 to 0.85; absolute effect: 37 fewer per 1000 over 1 year).[23]

Harms of the option: The meta-analysis of 4 studies (891 participants) found moderate quality evidence that did not rule out either an increase or a decrease in major bleeding (RR 0.68; 95% CI 0.1 to 4.78; absolute effect: 2 fewer per 1000).[23]

Values and preferences: The panel's judgment was that the typical patient would be against daily injections for duration of several months. Patients would view a potential reduction in mortality and symptomatic VTE favorably.

Resource use: The panel judged the costs to be acceptable when anticoagulation is for a relatively short time period (e.g., 3 months).

Other considerations: The panel judged the intervention to be acceptable given it is a relatively short time period. It was also judged as feasible given patients would be coming back anyway for catheter care.

Recommendation 3:

For outpatients with cancer and central venous catheters, the Saudi Expert Panel suggests thromboprophylaxis with parenteral anticoagulation. (weak recommendation; moderate quality evidence).

Remarks:

* Use a validated tool (e.g., the Khorana risk assessment score[29]) to risk stratify patients, as those at a higher risk for VTE are more likely to benefit.
* This recommendation does not apply to patients, who would otherwise have an indication for prophylaxis. Examples include: immobility, long-distance travel, highly thrombogenic drugs (e.g., thalidomide, lenalidomide, hormonal therapy, angiogenesis inhibitors).
* See separate recommendation for oral anticoagulation.

Question 4: Should oral anticoagulation versus no anticoagulation be used in patients with cancer and central venous catheters?

The summary of evidence (**Table 5**) is based on a systematic review by Akl et al.[23] The updated published report search identified 1 new trial that randomized patients with planned chemotherapy for cancer to no anticoagulant prophylaxis, LMWH, or warfarin 1 mg/d.[31]

Benefits of the option: The meta-analysis of 3 studies (1371 participants) found low quality evidence that did not rule out either an increase or a decrease in mortality (RR 0.97; 95% CI 0.82 to 1.15; absolute effect: 8 fewer per 1000 over 1 year).[23] The meta-analysis of 5 studies (1513 participants) found the moderate quality evi-

Table 5. Summary of findings, oral anticoagulation versus no oral anticoagulation be used in cancer patients with central venous catheters.

Patient or population: Patients with thrombosis prophylaxis in cancer patients with central venous catheters Settings: Outpatient or inpatient Intervention: VKA Comparison: No VKA					
Outcomes	**Illustrative comparative risks[a] (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**
	Assumed risk No VKA	**Corresponding risk** VKA			
Death	260 per 1000	252 per 1000 (213–298)	RR 0.97 (0.82–1.15)	1371 (3 studies)	Low
Symptomatic DVT	109 per 1000	55 per 1000 (32–97)	RR 0.51 (0.29–0.89)	1513 (5 studies)	Moderate
Major bleeding	2 per 1000	13 per 1000 (2–103)	RR 6.93 (0.86–56.08)	1093 (2 studies)	Low

CI, Confidence interval; DVT, deep vein thrombosis; LMWH, low molecular weight heparin; RR, Risk ratio; VKA, vitamin K antagonist; GRADE, Grading of Recommendations, Assessment, Development and Evaluation.

[a]The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

dence for reduction in VTE (RR 0. 51; 95% CI 0.29 to 0.89; absolute effect: 53 fewer per 1000 over 1 year).[23]

Harms of the option: The meta-analysis of 2 studies (1093 participants) found low quality evidence that did not rule out either an increase or a decrease in major bleeding (RR 6.93; 95% CI 0.86 to 56.08; absolute effect: 11 more per 1000).[23]

Values and preferences: The panel's judgment was that the typical patient would find oral anticoagulation burdensome due to the frequent testing and monitoring, diet and medication restrictions, stoppage for procedures, etc. Patients would view a potential reduction in mortality and symptomatic VTE favorably.

Resource use: The panel estimated the unit cost to be low. However, visits for monitoring and lab testing would require significant resources.

Other considerations: The panel judged the intervention to be acceptable given it is relatively short period. It was also judged as feasible given patients would be coming back anyway for catheter care.

Recommendation 4:

For outpatients with cancer and central venous catheters, the Saudi Expert Panel suggests against thromboprophylaxis with oral anticoagulation (weak recommendation; low quality evidence).

Remarks:

* Use a validated tool (e.g., the Khorana risk assessment score[29]) to risk stratify patients, as those at a higher risk for VTE are more likely to benefit
* This recommendation does not apply to patients, who would otherwise have an indication for prophylaxis. Examples include: immobility, long-distance travel, highly thrombogenic drugs (e.g., thalidomide, lenalidomide, hormonal therapy, angiogenesis inhibitors).
* Option could be offered to patients interested in thromboprophylaxis but averse to using injections (with LMWH).
* See separate recommendation for parenteral anticoagulation.

II. Antithrombotic therapy in patients with cancer

Question 5: Should LMWH versus UFH be used in patients with cancer being initiated on treatment for VTE?

The summary of evidence (**Table 6**) is based on a systematic review by Akl et al.[24] The updated published report search did not identify any new studies.

Benefits of the option: The meta-analysis of 11 studies (801 participants) found the low quality evidence for reduction in mortality (RR 0.71; 95% CI 0.52 to 0.98; absolute effect: 55 fewer per 1000 over 3 months).[24] The meta-analysis of 20 studies (6910 participants) found very low quality evidence suggesting a reduction in major bleeding (RR 0.67; 95% CI 0.45 to 1; absolute effect: 5 fewer per 1000 over 3 months).[24]

Harms of the option: The meta-analysis of 3 studies (371 participants) found low quality evidence that did not rule out either an increase or a decrease in VTE (RR 0.71; 95% CI 0.29 to 2.08; absolute effect: 21 fewer per 1000 over 3 months).[24]

Values and preferences: The panel judged that pa-

Table 6. Summary of Findings: low molecular weight heparin compared to unfractionated heparin for the initial treatment of venous thromboembolism in patients with cancer.

Patient or population: patients with the initial treatment of venous thromboembolism in patients with cancer Settings: Inpatient or outpatient Intervention: LMWH Comparison: UFH					
Outcomes[b]	Illustrative comparative risks[a] (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk UFH	Corresponding risk LMWH			
Death at 3 months Follow-up: median 3 months	189 per 1000	134 per 1000 (98 to 186)	RR 0.71 (0.52 to 0.98)	801 (11 studies)	Low
Recurrent VTE Follow-up: median 3 months	96 per 1000	75 per 1000 (28 to 200)	RR 0.78 (0.29 to 2.08)	371 (3 studies)	Low

CI: Confidence interval; LMWH: low molecular weight heparin; RR: Risk ratio; VTE: venous thromboembolism; UFH: unfractionated heparin; GRADE, Grading of Recommendations, Assessment, Development and Evaluation.

[a]The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b]Data on major bleeding, post-phlebitic syndrome and thrombocytopenia were not reported. There is indirect evidence that both LMWH and UFH increase the risk of major bleeding compared with no anticoagulation.

tients' preferences with relation to intravenous versus subcutaneous injections might vary, but the majority would value being discharged early.

Resource use: We did not identify any studies directly related to initial parenteral anticoagulation, so the panel relied on indirect evidence related to home treatment/early discharge of DVT. As stated earlier, health economic evaluations in both KSA[32,33] and non-KSA settings[34-40] conclude that home treatment of DVT is cost-saving.

Other considerations: The panel judged both interventions to be feasible and acceptable.

Recommendation 5:
In patients with cancer being initiated on treatment for venous thromboembolism, the Saudi Expert Panel suggests LMWH over intravenous UFH (weak recommendation; very low quality evidence).

Question 6: Should heparin versus oral anticoagulation be used in patients with cancer requiring long-term treatment of venous thromboembolism?

The summary of evidence is based on a Cochrane systematic review by Akl et al.[25] The updated published reports search identified a new trial comparing Idraparinux to standard therapy in the treatment of DVT in cancer patients.[41] Including the study in the meta-analysis did not substantially affect the results for mortality, VTE, or major bleeding. **Table 7** describes the summary of findings.[25,42-55]

Benefits of the option: The meta-analysis of 7 studies (2496 participants) found moderate quality evidence that did not rule out a reduction in mortality with LMWH compared with oral anticoagulation (RR 0.96; 95% CI 0.81 to 1.13; absolute effect: 7 fewer per 1000 over 6 months).[25,41] The meta-analysis of 8 studies (2727 participants) found the moderate quality evidence for reduction in VTE with LMWH compared with oral anticoagulation (RR 0.62; 95% CI 0.46 to 0.84).[25] The absolute effect varied by baseline risks associated with the stage of cancer; 30 fewer per 1000 over 6 months for patients with non-metastatic cancer and 76 fewer per 1000 over 6 months for patients with metastatic cancer.[25] One study provided the low quality evidence for reduction in post-thrombotic syndrome with LMWH compared with oral anticoagulation (RR 0.85; 95% CI 0.77 to 0.94; absolute effect: 30 fewer per 1000 over 2 years).[25,41]

Harms of the option: The meta-analysis of 8 studies (2737 participants) found moderate quality evidence that did not rule out either an increase or a decrease in major bleeding (RR 0.81; 95% CI 0.55 to 1.2).[25] The absolute effect varied by baseline risks associated with the stage of cancer; 4 fewer per 1000 over 6 months for patients with non-metastatic cancer and 15 fewer per 1000 over 6 months for patients with metastatic cancer.[25,41]

Values and preferences: The panel's judgment was that patients might assign different values to the burden of warfarin versus LMWH. They typically assigned a high value to avoiding post-thrombotic syndrome.

Resource use: The panel's judgment was that LMWH is more expensive than warfarin. Warfarin requires monitoring, testing, and frequent visits to the clinic.

Monitoring and evaluation: The Saudi Panel recommended close monitoring for vitamin K antagonist (VKA) therapy and monitoring of renal function and platelet count for LMWH therapy.

Other considerations: The panel judged LMWH to be both feasible and acceptable given its current use in practice.

Recommendation 6:
In patients with metastatic cancer requiring long-term treatment of VTE, the Saudi Expert Panel recommends LMWH over VKA. (strong recommendation; moderate quality evidence).

In patients with non-metastatic cancer requiring long-term treatment of venous thromboembolism, the Saudi Expert Panel suggests LMWH over VKA. (weak recommendation; moderate quality evidence)

Remarks:

* Patients who are apprehensive about injections may prefer VKA over LMWH.
* Patients who choose VKA will require closer monitoring.

DISCUSSION

This clinical practice guideline provides guidance on VTE prophylaxis and treatment in cancer patients. It is a part of the larger initiative of the Saudi MoH aiming at reducing variability in clinical practice across Saudi Arabia. The target audience includes primary care physicians and specialists in Emergency Medicine, Internal Medicine, and Hematology/Oncology. Other health care professionals, public health officers, and policy makers may also benefit from it. This guideline is not intended to provide a standard of care. It provides clinicians and their patients with the basis for rational decisions. Clinicians, patients, third-party payers, institutional review committees, other stakeholders, and courts should never view the recommendations in this guideline as dictates. No guideline can take into account all of the unique features of individual clinical circum-

stances. The remarks accompanying each recommendation are integral parts and serve to facilitate its accurate interpretation. They should never be omitted when quoting or translating recommendations from this guideline.

This guideline did not cover all the scenarios of VTE prophylaxis and treatment in patients with cancer. The questions were selected based on a formal prioritization process. The recommendations in this guideline shared similarities with those of other societies and panels. Similar to the first recommendation, the American Society of Clinical Oncology does not recommend routine anticoagulant prophylaxis of ambulatory cancer patients except for patients on thalidomide or lenalidomide.[56] The American Society of Clinical Oncology and an international consensus working group recommended initiation of VTE treatment with LMWH as in the fifth recommendation of this guideline.[57,58] This guideline suggested against routine VTE prophylaxis in cancer patients with central venous catheters similar to the 9th edition of the Antithrombotic Therapy and Prevention of Thrombosis.[59] However, this guideline did not address VTE prophylaxis for patients undergoing major cancer surgery. The American Society of Clinical Oncology recommended that such patients should start prophylaxis before surgery, continuing it for at least 7 to 10 days and considering the extension of

Table 7. Summary of findings: Heparin versus oral anticoagulation in patients with cancer requiring long-term treatment of venous thromboembolism.

Patient or population: Patients with long term treatment of patients with VTE Settings: Outpatient Intervention: LMWH Comparison: VKA					
Outcomes	**Illustrative comparative risks[a] (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**
	Assumed risk VKA	**Corresponding risk LMWH**			
Death Follow-up, median 6 mo	164 per 1000	158 per 1000 (133–185)	RR 0.96 (0.81–1.13)	2496 (7 studies)	Moderate
Recurrent VTE Follow-up: median 6 mo	Low[b]		RR 0.62 (0.46–0.84)	2727 (8 studies)	Moderate
	30 per 1000	19 per 1000 (14–25)			
	Moderate[b]				
	80 per 1000	50 per 1000 (37–67)			
	High[b]				
	200 per 1000	124 per 1000 (92–168)			
Major bleeding Follow-up: median 6 mo	Low[c]		RR 0.81 (0.55–1.2)	2737 (8 studies)	Moderate
	20 per 1000	16 per 1000 (11–24)			
	High[d]				
	80 per 1000	65 per 1000 (44–96)			
Post-phlebitic syndrome Self-reported leg symptoms and signs Follow-up: median 2 y	Moderate		RR 0.85 (0.77–0.94)	100 (1 study)	Low
	200 per 1000	170 per 1000 (154–188)			

CI, Confidence interval; LMWH, low molecular weight heparin; RR, risk ratio; VKA, vitamin K antagonist; VTE, venous thromboembolism; UFH, unfractionated heparin; GRADE, Grading of Recommendations, Assessment, Development and Evaluation.

[a]The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b]Low risk of recurrent VTE corresponds to patients without cancer, intermediate risk of recurrent VTE corresponds to patients with local or recently resected cancer, and high risk of recurrent VTE corresponds to patients with locally advanced or distant metastatic cancer

[c]Low risk of bleeding corresponds to the absence of any risk factor for bleeding (i.e., age >75 y; cancer; metastatic disease; chronic renal or hepatic failure; platelet count <80,0000; antiplatelet therapy; history of bleeding without a reversible cause).

[d]High risk of bleeding corresponds to the presence of at least 1 risk factor for bleeding (i.e., age >75 y, cancer, metastatic disease, chronic renal or hepatic failure, platelet count < 800 000, antiplatelet therapy, history of bleeding without a reversible cause)

prophylaxis for up to 4 weeks in high-risk patients.[57] The 9th edition of the Antithrombotic Therapy and Prevention of Thrombosis recommended postoperative prophylaxis with LMWH for 4 weeks for patients at a high risk for VTE undergoing abdominal or pelvic surgery for cancer.[60] This guideline also did not address extended anticoagulant therapy for patients with VTE and active cancer, which was recommended in the 9th edition of the Antithrombotic Therapy and Prevention of Thrombosis.[61]

The evidence used in the making of this guideline was frequently of low to moderate quality.[21-25] Evidence coming from Saudi Arabia was also scarce. The Saudi Expert Panel suggested local research on the values and preferences of the Saudi population, including those who have cancer, regarding VTE treatment with the various modalities and the potential side effects from such treatments. The Panel advocated the performance of studies that identify which types and stages of cancer were more likely to benefit from thromboprophylaxis and those that evaluate the economic aspect of the different VTE treatment strategies in cancer patients.

This guideline is on VTE prophylaxis and treatment in patients with cancer. In conclusion, the Saudi Expert Panel suggests against routine thromboprophylaxis with heparin and recommends against it with oral anticoagulants for outpatients with cancer. The panel suggests parenteral but not oral anticoagulant thromboprophylaxis in those who have central venous catheters. Additionally, the panel suggests LMWH over intravenous UFH for the initial VTE treatment and recommends LMWH over VKA for the long-term VTE treatment.

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