وزارة الصحة
Ministry of Health


The Saudi Center for
Evidence Based Health Care

# Venous Thromboembolism

## Clinical Practice Guideline on the Treatment of Venous Thromboembolism

April 2014

# Venous Thromboembolism

## Clinical Practice Guideline on the Treatment of Venous Thromboembolism

April 2014

# Guideline Adaptation Panel Members

## Saudi Expert Panel

Dr. Abdulkarim Al Momen
Dr. Furjah Algahtani
Dr. Hazzaa Al Zahrani
Dr. Khalid Al Saleh
Dr. Mohammed Al Sheef
Dr. Tareq Owaidah

The Saudi Scientific Hematology Society

## McMaster Working Group

Elie A Akl, Waleed Alhazzani, Ignacio Neumann, Wojtek Wiercioch, Jan Brozek, and Holger Schünemann, on behalf of the McMaster Guideline Working Group

**Address for correspondence:**
The Saudi Center for Evidence Based Health Care
E-mail: ebhc@moh.gov.sa

**Disclosure of potential conflict of interest:**
Dr. Farjah Algahtani declared involvement in two international studies sponsored by Sanofi and Leo respectively, and giving lectures on behalf of Sanofi. Dr. Hazza Abdullah Alzahrani declared giving presentations on behalf of Leo Pharma Novartis CSL. Dr. Tarek Owaidah declared receiving sponsorships for scientific meetings by Bayer, Stago, and Novo Nordics, honoraria as speaker for Bayer, CLS Behring, and Alexion. He also declared commercial business interest in the National Blood and Cancer Center.
Other co-authors have declared no conflict of interest.

**Funding:**
This clinical practice guideline was funded by the Ministry of Health, Saudi Arabia.

**Abbreviations:**

DVT: deep vein thrombosis
EtR: evidence-to-recommendation
GRADE: Grading of Recommendations, Assessment, Development and Evaluation
KSA: Kingdom of Saudi Arabia
LMWH: low molecular weight heparinNOACs: new oral anticoagulants
PE: pulmonary embolism
VKA: vitamin K antagonist
VTE: venous thromboembolism
UFH: unfractionated Hepari

# Contents

# Executive summary

## Introduction

Venous thromboembolism is a relatively common disease that is associated with significant morbidity and mortality, and significant health expenditures. Also, patients with cancer are at particularly high risk of developing venous thromboembolism. Given the importance of this topic, the Ministry of Health of the Kingdom of Saudi Arabia with the methodological support of the McMaster University working group produced clinical practice guidelines to assist health care providers in evidence-based clinical decision-making on the prevention and treatment of thromboembolic disease.

## Methodology

This clinical practice guideline is a part of the larger initiative of the Ministry of Health (MoH) of the Kingdom of Saudi Arabia (KSA) to establish a program of rigorous adaptation and de novo development of guidelines. The ultimate goals are to provide guidance for clinicians and reduce variability in clinical practice across the Kingdom.

The KSA guideline panel selected the topic of this guideline and all clinical questions addressed herein using a formal prioritization process. For all selected questions we updated existing systematic reviews that were used for the "Antithrombotic Therapy for VTE Disease" chapter of the 2012 Antithrombotic Therapy and Prevention of Thrombosis guidelines, 9th edition. We also conducted systematic searches for information that was required to develop full guidelines for the KSA, including searches for information about patients' values and preferences and cost (resource use) specific to the Saudi context. Based on the updated systematic reviews we prepared summaries of available evidence supporting each recommendation following the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach. We used this information to prepare the *evidence to recommendation tables* used by the guideline panel to follow a structured consensus process and transparently document all decisions made during the meeting (see **Appendix 1**). The guideline panel met in Riyadh on December 3, 2013 and formulated all recommendations during this meeting. Potential conflicts of interests of all panel members were managed according to the World Health Organization (WHO) rules.

## How to use these guidelines

The guideline working group developed and graded the recommendations and assessed the quality of the supporting evidence according to the GRADE approach. Quality of evidence (confidence in the available estimates of treatment effects) is categorized as: high, moderate, low, or very low based on consideration of risk of bias, directness, consistency and precision of the estimates. High quality evidence indicates that we are very confident that the *true* effect lies close to that of the estimate of the effect. Moderate quality evidence indicates moderate confidence, and that the *true* effect is likely close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality evidence indicates that our confidence in the effect estimate is limited, and that the *true* effect may be substantially different. Finally, very low quality evidence indicates that the estimate of effect of interventions is very uncertain, the *true* effect is likely to be substantially different from the effect estimate and further research is likely to have important potential for reducing the uncertainty.

The strength of recommendations is expressed as either strong ('guideline panel recommends…') or conditional ('guideline panel suggests…') and has explicit implications (see **Table 1**). Understanding the interpretation of these two grades is essential for sagacious clinical decision making.

**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. |

## Key questions

1. Should home treatment vs. hospital treatment be used for patients with acute DVT of the leg?
2. Should early discharge vs. standard discharge be used for patients with acute PE?
3. Should heparin vs no heparin be used in outpatients with cancer who have no other therapeutic or prophylactic indication for anticoagulation?
4. Should oral anticoagulation vs no oral anticoagulation be used in outpatients with cancer who have no other therapeutic or prophylactic indication for anticoagulation?
5. Should parenteral anticoagulation vs no anticoagulation be used in patients with cancer and central venous catheters?
6. Should oral anticoagulation vs no anticoagulation be used in patients with cancer and central venous catheters?
7. Should Low Molecular Weight Heparin (LMWH) vs Unfractionated Heparin (UFH) be used in patients with cancer being initiated on treatment for venous thromboembolism?
8. Should heparin vs oral anticoagulation be used in patients with cancer requiring long term treatment of venous thromboembolism?

## Recommendations

**Recommendation 1:**
**For patients with simple acute DVT of the leg, the Ministry of Health of Saudi Arabia guideline panel suggests home treatment over hospital treatment (conditional recommendation; moderate quality evidence)**

*Remarks:*

- Ensure that patients have support from family, access to a phone, access to a physician, and the ability to get to a hospital in a reasonable time if needed
- Consider patient level of education, knowledge about the disease, and likelihood of compliance
- Consider hospital treatment for patients with severe acute DVT of the

leg and patients who are apprehensive
- This recommendation applies to anticoagulation treatment with LMWH but not NOACs

**Recommendation 2:**
**For patients with low risk acute PE, the Ministry of Health of Saudi Arabia guideline panel suggests early discharge over late discharge (conditional recommendation; moderate quality evidence)**

*Remarks:*
- Use a validated prediction rule (e.g. Pulmonary Embolism Severity Index) to risk stratify patients
- Ensure that patients have a close follow-up appointment
- Ensure that patients have support from family, access to a phone, access to a physician, and the ability to get to a hospital in a reasonable time if needed
- Consider patient level of education, knowledge about the disease, and likelihood of compliance
- Consider hospital treatment for patients with severe acute DVT of the leg and patients who are apprehensive
- This recommendation applies to anticoagulation treatment with LMWH but not NOACs
- Highly selected cases be discharged home as opposed to being admitted and discharged early

**Recommendation 3:**
**For outpatients with cancer, the Ministry of Health of Saudi Arabia guideline panel suggests against thromboprophylaxis with heparin (conditional recommendation; moderate quality evidence)**

*Remarks:*
- Use a validated tool (e.g., Khorana JNCCN 2011;9:789-798) to risk stratify patients, as those at 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

**Recommendation 4:**
**For outpatients with cancer, the Ministry of Health of Saudi Arabia guideline 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

**Recommendation 5:**
**For outpatients with cancer and CVC, the Ministry of Health of Saudi Arabia guideline panel suggests thromboprophylaxis with parenteral anticoagulation (weak recommendation; moderate quality evidence)**

*Remarks:*
- Use a validated tool (e.g., Khorana JNCCN 2011;9:789-798) to risk stratify patients, as those at 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

**Recommendation 6:**
**For outpatients with cancer and CVC, the Ministry of Health of Saudi Arabia guideline panel suggests against thromboprophylaxis with oral anticoagulation (weak recommendation; low quality evidence)**

*Remarks:*

- Use a validated tool (e.g., Khorana JNCCN 2011;9:789-798) to risk stratify patients, as those at 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

**Recommendation 7:**
**In patients with cancer being initiated on treatment for venous thromboembolism, the Ministry of Health of Saudi Arabia guideline panel suggests LMWH over IV UFH (conditional recommendation; very low quality evidence)**

**Recommendation 8:**
**In patients with metastatic cancer requiring long term treatment of venous thromboembolism, the Ministry of Health of Saudi Arabia panel recommends LMWH over VKA (strong recommendation; moderate quality evidence)**
**In patients with non-metastatic cancer requiring long term treatment of venous thromboembolism, the Ministry of Health of Saudi Arabia 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.

# Scope and purpose

The purpose of this document is to provide guidance about selected clinical questions on the prevention and treatment of thromboembolic disease. The target audience of these guidelines includes primary care physicians and specialists in emergency medicine, internal medicine, and medical oncology in the Kingdom of Saudi Arabia. Other health care professionals, public health officers and policy makers may also benefit from these guidelines. This clinical practice guideline is a part of the larger initiative of the Ministry of Health of Saudi Arabia to establish a program of rigorous adaptation and de novo development of guidelines in the Kingdom; the ultimate goal being to provide guidance for clinicians and reduce variability in clinical practice across the Kingdom.

# Introduction

The Ministry of Health of the KSA, with the methodological support of the McMaster University working group, initiated a project to develop and adapt practice guidelines for the KSA to assist health care providers in evidence-based clinical decision-making. This included guidelines for the prevention and treatment of thromboembolic disease.

Venous thromboembolism (VTE) is a relatively common disease that is associated with significant morbidity and mortality. It is also associated with health expenditures given patients diagnosed with the condition are typically admitted for inpatient management and typically require long-term therapy.

Patients with cancer are at particularly high risk of developing VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE). In addition to the malignancy itself, chemotherapy, radiotherapy, hormonal therapy, as well as indwelling central catheters increase the risk of thrombosis.

The recommendations cover the following topics: outpatient versus inpatient management of venous thromboembolism (2 recommendations), thromboprophylaxis in patients with cancer (4 recommendations), and thrombotic therapy in patients with cancer (2 recommendations).

# Methodology

To facilitate the interpretation of these guidelines; we briefly describe the methodology we used to develop and grade recommendations and quality of the supporting evidence. We present the details of the methodology in a separate publication.[2]

***Overall process***

Members of the McMaster guideline working group as well as the KSA guideline panel were involved in this process. The KSA guideline panel selected the topic of this guideline and all clinical questions addressed herein using a formal prioritization process. For all selected questions we updated existing systematic reviews that were used for the "Antithrombotic Therapy for VTE Disease" chapter of the Antithrombotic Therapy and Prevention of Thrombosis guidelines, 9th edition (see **Appendix 2**).[1] For each question, the McMaster guideline working group updated the search strategy to identify new studies and/or new systematic reviews. When relevant, the meta-analyses were updated. We also conducted systematic searches for information that was required to develop full guidelines for the KSA, including searches for information about patients' values and preferences and cost (resource use) specific to the Saudi context.

Next, the McMaster guideline leader (EAA) developed for each question a summary of findings table and an evidence-to-recommendation (EtR) table and shared them with the panel members (see **Appendix 1**). 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 met and formulated all recommendations during this meeting. Potential conflicts of interests of all panel members were managed according to the World Health Organization (WHO) rules.[3]

***Grading of the quality of evidence***

The GRADE working group defines the quality of evidence as the extent of our confidence that the estimate of an effect is adequate to support a particular decision or recommendation.[4] We assessed the quality of evidence using the GRADE approach.[5]

Quality of evidence is 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:

- *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 of 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.[6] According to the GRADE approach, the strength of a recommendation is either strong or conditional (weak) and has explicit implications (see **Table 1**).[6] Understanding the interpretation of these two grades – either strong or conditional – of the strength of recommendations is essential for sagacious clinical decision-making.

# How to use these guidelines

The Ministry of Health of Saudi Arabia and McMaster University Clinical Practice Guidelines on the management of venous thromboembolism are not intended to provide a standard of care. They provide clinicians and their patients with the basis for rational decisions. Clinicians, patients, third-party payers, institutional review committees, other stakeholders, or the courts should never view these recommendations as dictates. No guidelines or recommendations can take into account all of the often-compelling unique features of individual clinical circumstances. Therefore, no one charged with evaluating clinicians' actions should attempt to apply the recommendations from these guidelines by rote or in a blanket fashion.

Qualifying remarks accompanying each recommendation are its integral parts and serve to facilitate an accurate interpretation. They should never be omitted when quoting or translating recommendations from these guidelines.

# Key questions

The following is a list of the clinical questions selected by the KSA 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.[2]

1. Should home treatment vs. hospital treatment be used for patients with acute DVT of the leg?

2. Should early discharge vs. standard discharge be used for patients with acute PE?
3. Should heparin vs no heparin be used in outpatients with cancer who have no other therapeutic or prophylactic indication for anticoagulation?
4. Should oral anticoagulation vs no oral anticoagulation be used in outpatients with cancer who have no other therapeutic or prophylactic indication for anticoagulation?
5. Should parenteral anticoagulation vs no anticoagulation be used in patients with cancer and central venous catheters?
6. Should oral anticoagulation vs no anticoagulation be used in patients with cancer and central venous catheters?
7. Should Low Molecular Weight Heparin (LMWH) vs Unfractionated Heparin (UFH) be used in patients with cancer being initiated on treatment for venous thromboembolism?
8. Should heparin vs oral anticoagulation be used in patients with cancer requiring long term treatment of venous thromboembolism?

# Recommendations

**I. Outpatient versus inpatient management of venous thromboembolism**

**Question 1: Should home treatment vs. hospital treatment be used for patients with acute DVT of the leg?**

*Summary of Findings:*
The summary of evidence was based on a Cochrane systematic review by Othieno et al.[7] The updated literature search identified one new study conducted by Algahtani et al. in Saudi Arabia.[8] The new study was included in the updated meta-analysis.

*Benefits of the Option:*
The meta-analysis of 7 trials (total of 1769 participants) found moderate quality evidence that home treatment of DVT reduces recurrent VTE (RR 0.65; 95% CI 0.44 to 0.94; absolute effect: 27 fewer events per 1000). The meta-analysis of 6 studies (total of 1708 participants; absolute effect: 7 fewer events per 1000) found low quality evidence that home treatment of DVT reduces major bleeding (RR 0.67; 95% CI 0.33 to 1.36).

*Harms of the Option:*
It is unclear what the effects of home treatment of DVT on mortality (RR 0.72; 95% CI 0.45 to 1.15) and quality of life are.

*Values and Preferences:*
Values and preferences may vary. Some patients and carers would prefer for the patient to be admitted. Some others would prefer to be discharged if they know they could easily access a physician.

*Resource Use:*
Health economic evaluations in settings different from that of Saudi Arabia conclude that home treatment is cost-saving (around US$500 to US$2500 per patient).[9-15] We identified two studies conducted in the KSA setting. Algahtani conducted a prospective study of 61 DVT cases presenting to ED (Aug 2009-Aug 2010) of King Khalid University Hospital (KKUH).[8] The mean outpatient cost was significantly lower ($1750 vs. $4338). Aleissi conducted a retrospective chart analysis of DVT cases managed between 2005 and 2012 at King Abdulaziz Medical City (KAMC).[16] Of 190 DVT cases, 80 (42%) were eligible for outpatient management. The authors concluded that 78.75 bed days would have been saved per year and cost savings would be SR 118,125 per year.

*Other Considerations:*
The panel judged home treatment of DVT to be acceptable to physicians and the Ministry of Health. However, they were concerned with the lack of ultrasound service after 4:30pm and on weekends in emergency rooms.

**Recommendation 1:**

For patients with simple acute DVT of the leg, the Ministry of Health of Saudi Arabia guideline panel suggests home treatment over hospital treatment (conditional recommendation; moderate quality evidence)

*Remarks:*

- Ensure that patients have support from family, access to a phone, access to a physician, and the ability to get to a hospital in a reasonable time if needed
- Consider patient level of education, knowledge about the disease, and likelihood of compliance
- Consider hospital treatment for patients with severe acute DVT of the leg and patients who are apprehensive
- This recommendation applies to anticoagulation treatment with LMWH but not NOACs

*Implementation Considerations:*

- Need to make ultrasound services to assess DVT diagnosis available after 4:30pm and during weekends
- Need to have in place 24-hour clinic coverage for these patients (e.g. thrombosis services)

*Monitoring and Evaluation:*

- Evaluate the impact of implementation on outcomes and costs
- Percentage of patients treated at home versus hospital

*Research Priorities:*

- Determine local rates of events (recurrent VTE, major bleeding)
- Assess effects of home treatment versus hospital treatment on post-thrombotic syndrome

**Question 2: Should early discharge vs. standard discharge be used for patients with acute PE?**

*Summary of Findings:*

The summary of evidence is based on a systematic review Otero et al [17] and a more recent trial by Aujesky et al [18]. The updated literature search identified one new systematic review by Piran et al.[19] That review

did not identify any trial not already considered.

*Benefits and Harms of the Option:*

The meta-analysis of 2 trials (total of 471 participants) found moderate quality evidence of possible increase in VTE (RR 1.23; 95% CI 0.25 to 6.03) and major bleeding (RR 2.74; 95% CI 0.45 to 16.71). However, these trials found that any absolute increase in these outcomes would be of small size given the low baseline risks (2 more VTE per 1000 and 8 more major bleeding per 1000 over a 3 months period). Observational data confirms low risk of recurrent VTE in patients with low risk acute PE.[19]

*Values and Preferences:*

Values and preferences may vary. Some patients and carers would prefer for the patient to be admitted. Some others would prefer to be discharged if they know they could easily access a physician.

*Resource Use:*

We did not identify any studies directly related to PE, so the panel relied on indirect evidence related to DVT. As stated earlier, health economic evaluations in both KSA [8,16] and non-KSA settings [9-15] conclude that home treatment of DVT is cost-saving.[9-15]

*Other Considerations:*

The panel judged that the acceptability of early discharge might vary by physician. Some of them might be apprehensive to releasing patients early given the gravity of the condition. Early discharge is potentially feasible but requires 24-hour clinic coverage for the patients.

**Recommendation 2:**

For patients with low risk acute PE, the Ministry of Health of Saudi Arabia guideline panel suggests early discharge over late discharge (conditional recommendation; moderate quality evidence)

*Remarks:*

- Use a validated prediction rule (e.g. Pulmonary Embolism Severity Index) to risk stratify patients
- Ensure that patients have a close follow-up appointment
- Ensure that patients have support from family, access to a phone, access to a physician, and the ability to get to a hospital in a reasonable time if needed
- Consider patient level of education, knowledge about the disease, and likelihood of compliance
- Consider hospital treatment for patients with severe acute DVT of the leg and patients who are apprehensive
- This recommendation applies to anticoagulation treatment with LMWH but not NOACs
- Highly selected cases be discharged home as opposed to being admitted and discharged early

*Implementation Considerations:*

- Need to have in place 24-hour clinic coverage for these patients (e.g. thrombosis services)

*Monitoring and Evaluation:*

- Evaluate the impact of implementation on outcomes and costs
- Percentage of patients discharged early versus late

*Research Priorities:*

- Determine local rates of events (recurrent VTE, major bleeding)
- Assess effects of early discharge on chronic thromboembolic disease, pulmonary hypertension

**II. Thromboprophylaxis in patients with cancer**

**Question 3: Should heparin vs no heparin be used in outpatients with cancer who have no other therapeutic or prophylactic indication for anticoagulation?**

*Summary of Findings:*

The summary of evidence is based on a Cochrane systematic review by Akl et al[20]. The updated literature search identified three additional studies that were included in the meta-analyses.[21-23] Subgroup analyses by type or stage of cancer were either not feasible or inconclusive.

*Benefits of the Option:*

The meta-analysis of 13 studies (7266 participants) found moderate quality evidence of reduction in mortality (RR 0.95; 95% CI 0.89 to 1.00; absolute effect: 23 fewer per 1000 over one year). The meta-analysis of 12 studies (6998 participants) found high quality evidence of reduction in VTE (RR 0.65; 95% CI 0.43 to 0.74; absolute effect: 23 fewer per 1000 over one year).

*Harms of the Option:*

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

*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 potential reduction in mortality and symptomatic VTE favorably.

*Resource Use:*

The panel estimated the cost at SR 20 per injection per day (a small unit cost). Applied to the population level for a period of 6 months

for 13,000 patients: SR 46 .8 Million. 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 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 3:**

For outpatients with cancer, the Ministry of Health of Saudi Arabia guideline panel suggests against thromboprophylaxis with heparin (conditional recommendation; moderate quality evidence)

*Remarks:*

- Use a validated tool (e.g., Khorana JNCCN 2011;9:789-798) to risk stratify patients, as those at 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

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

*Research Priorities:*

- Identify which types and stages of cancer are more likely to benefit (individual patient data meta-analysis is currently being conducted)
- Assess cost effectiveness

**Question 4: Should oral anticoagulation vs no oral anticoagulation be used in outpatients with cancer who have no other therapeutic or prophylactic indication for anticoagulation?**

*Summary of Findings:*
The summary of evidence is based on a Cochrane systematic review by Akl et al.[24] The updated literature search identified one additional phase II trial comparing apixaban to placebo. The trial included patients with cancer receiving chemotherapy and who are at increased risk for thrombosis. 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 one year). One study (315 participants) found moderate quality evidence of reduction in VTE (RR 0.15; 95% CI 0.02 to 1.2; absolute effect: 25 fewer per 1000 over one year).

*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). 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).

*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 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 as probably not acceptable because of lack of effectiveness (no effect on mortality) and cost-effectiveness.

**Recommendation 4:**

For outpatients with cancer, the Ministry of Health of Saudi Arabia guideline 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

*Research Priorities:*

- Conduct studies in high-risk patients
- Conduct studies to test new oral anticoagulants.

**Question 5: Should parenteral anticoagulation vs no anticoagulation be used in patients with cancer and central venous catheters?**

*Summary of Findings:*
The summary of evidence is based on a systematic review by Akl et al.[25] The updated literature search identified one new trial that randomized patients with planned chemotherapy for cancer to no anticoagulant prophylaxis, LMWH or warfarin 1 mg/day.[26]

*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 decrease in mortality (RR 0.85; 95% CI 0.55 to 1.31; absolute effect: 10 fewer per 1000 over one year). The meta-analysis of 7 studies (1455 participants) found high quality evidence of reduction in VTE (RR 0.54; 95% CI 0.35 to 0.85; absolute effect: 37 fewer per 1000 over one year).

*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 decrease in major bleeding (RR 0.68; 95% CI 0.1 to 4.78; absolute effect: 2 fewer per 1000).

*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 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 5:**

For outpatients with cancer and CVC, the Ministry of Health of Saudi Arabia guideline panel suggests thromboprophylaxis with parenteral anticoagulation (weak recommendation; moderate quality evidence)

Remarks:

- Use a validated tool (e.g., Khorana JNCCN 2011;9:789-798) to risk stratify patients, as those at 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

*Research Priorities:*
- Studies comparing new oral anticoagulants vs. heparin
- KSA cost-effectiveness studies

**Question 6: Should oral anticoagulation vs no anticoagulation be used in patients with cancer and central venous catheters?**

*Summary of Findings:*
The summary of evidence is based on a systematic review by Akl et al.[25] The updated literature search identified one new trial that randomized patients with planned chemotherapy for cancer to no anticoagulant prophylaxis, LMWH or warfarin 1 mg/day.[26]

*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 decrease in mortality (RR 0.97; 95% CI 0.82 to 1.15; absolute effect: 8 fewer per 1000 over one year). The meta-analysis of 5 studies (1513 participants) found moderate quality evidence of reduction in VTE (RR 0. 51; 95% CI 0.29 to 0.89; absolute effect: 53 fewer per 1000 over one year).

*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 decrease in major bleeding (RR 6.93; 95% CI 0.86 to 56.08; absolute effect: 11 more per 1000).

*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 potential reduction in mortality and symptomatic VTE favorably.

*Resource Use:*
The panel estimated the unit cost to be low. However, visits for monitoring, 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 6:**

For outpatients with cancer and CVC, the Ministry of Health of Saudi Arabia guideline panel suggests against thromboprophylaxis with oral anticoagulation (weak recommendation; low quality evidence)

Remarks:
- Use a validated tool (e.g., Khorana JNCCN 2011;9:789-798) to risk stratify patients, as those at 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

*Research Priorities:*

- Research about new oral anticoagulants;
- Studies comparing new oral anticoagulants vs. heparin
- KSA cost-effectiveness studies

**III. Thrombotic therapy in patients with cancer**

**Question 7: Should Low Molecular Weight Heparin (LMWH) vs Unfractionated Heparin (UFH) be used in patients with cancer being initiated on treatment for venous thromboembolism?**

*Summary of Findings:*
The summary of evidence is based on a systematic review by Akl et al.[27] The updated literature search did not identify any new studies.

*Benefits and harms of the Option:*
The meta-analysis of 11 studies (801 participants) found low quality evidence of reduction in mortality (RR 0.71; 95% CI 0.52 to 0.98; absolute effect: 55 fewer per 1000 over 3 months). The meta-analysis of 3 studies (371 participants) found low quality evidence that did not rule out either an increase or decrease in VTE (RR 0.71; 95% CI 0.29 to 2.08; absolute effect: 21 fewer per 1000 over 3 months). The meta-analysis of 20 studies (6910 participants) found very low quality evidence suggesting reduction in major bleeding (RR 0.67; 95% CI 0.45 to 1; absolute effect: 5 fewer per 1000 over 3 months).

*Values and Preferences:*
The panel judged that patients' 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 [8,16] and non-KSA settings [9-15] conclude that home treatment of DVT is cost-saving.[9-15]

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

**Recommendation 7:**

In patients with cancer being initiated on treatment for venous thromboembolism, the Ministry of Health of Saudi Arabia guideline panel suggests LMWH over IV UFH (conditional recommendation; very low quality evidence)

*Research Priorities:*

- Studies comparing LMWH to IV UFH
- Studies comparing initiation of VTE treatment with heparin versus NOACs

**Question 8: Should heparin vs oral anticoagulation be used in patients with cancer requiring long term treatment of venous thromboembolism?**

*Summary of Findings:*
The summary of evidence is based on a Cochrane systematic review by Akl et al.[28] The updated literature search identified a new trial comparing Idraparinux to standard therapy in the treatment of DVT in cancer patients. Including the study in the meta-analysis did not substantially affect the results for mortality, VTE, or major bleeding.[29]

*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). The meta-analysis of 8 studies (2727 participants) found

moderate quality evidence of reduction in VTE with LMWH compared with oral anticoagulation (RR 0.62; 95% CI 0.46 to 0.84). 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. One study provided 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).

*Harms of the Option:*
The meta-analysis of 8 studies (2737 participants) found moderate quality evidence that did not rule our either an increase or a decrease in major bleeding (RR 0.81; 95% CI 0.55 to 1.2). 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.

*Values and Preferences:*
The panel's judgment was that patients might assign different values to the burden of warfarin versus LMWH. They typically assign a high value to avoiding PTS.

*Resource Use:*
The panel's judgment was that LMWH is more expensive than warfarin. Warfarin requires
*Implementation Considerations:*

- Consistent with current practice, nothing required at administrative level.

*Monitoring and Evaluation:*

- Close monitoring for VKA therapy
- Monitoring of renal function and platelet count for LMWH therapy.

*Research Priorities:*

- New oral anticoagulants vs. LMWH

monitoring, testing, and frequent visits to the clinic.

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

**Recommendation 8:**

In patients with metastatic cancer requiring long term treatment of venous thromboembolism, the Ministry of Health of Saudi Arabia panel recommends LMWH over VKA (strong recommendation; moderate quality evidence)

In patients with non-metastatic cancer requiring long term treatment of venous thromboembolism, the Ministry of Health of Saudi Arabia 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.

*Subgroup Considerations:*

- By cancer status (metastatic versus non-metastatic) as detailed above

# References


1. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* Feb 2012;141(2 Suppl):e419S-494S.
2. McMaster University Guideline Working Group. *Methodology for the Development of the Ministry of Health of Saudi Arabia and McMaster University Clinical Practice Guidelines.* 2014.
3. World Health Organization. WHO Handbook for Guideline Development. 2012; http://apps.who.int/iris/bitstream/10665/75146/1/9789241548441_eng.pdf. Accessed February 7, 2014.
4. Balshem H, Helfand M, Schunemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *Journal of clinical epidemiology.* Apr 2011;64(4):401-406.
5. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *Journal of clinical epidemiology.* Apr 2011;64(4):383-394.
6. Andrews J, Guyatt G, Oxman AD, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. *Journal of clinical epidemiology.* Jul 2013;66(7):719-725.
7. Othieno R, Abu Affan M, Okpo E. Home versus in-patient treatment for deep vein thrombosis. *The Cochrane database of systematic reviews.* 2007(3):CD003076.
8. Algahtani F, Aseri ZA, Aldiab A, Aleem A. Hospital versus home treatment of deep vein thrombosis in a tertiary care hospital in Saudi Arabia: Are we ready? *Saudi pharmaceutical journal : SPJ : the official publication of the Saudi Pharmaceutical Society.* Apr 2013;21(2):165-168.
9. Backman K, Carlsson P, Kentson M, Hansen S, Engquist L, Hallert C. Deep venous thrombosis: a new task for primary health care. A randomised economic study of outpatient and inpatient treatment. *Scand J Prim Health Care.* Mar 2004;22(1):44-49.
10. O'Brien B, Levine M, Willan A, et al. Economic evaluation of outpatient treatment with low-molecular-weight heparin for proximal vein thrombosis. *Arch Intern Med.* Oct 25 1999;159(19):2298-2304.
11. Huse DM, Cummins G, Taylor DC, Russell MW. Outpatient treatment of venous thromboembolism with low-molecular-weight heparin: an economic evaluation. *Am J Manag Care.* Jan 2002;8(1 Suppl):S10-16.
12. Spyropoulos AC, Hurley JS, Ciesla GN, de Lissovoy G. Management of acute proximal deep vein thrombosis: pharmacoeconomic evaluation of outpatient treatment with enoxaparin vs inpatient treatment with unfractionated heparin. *Chest.* Jul 2002;122(1):108-114.
13. Tillman DJ, Charland SL, Witt DM. Effectiveness and economic impact associated with a program for outpatient management of acute deep vein thrombosis in a group model health maintenance organization. *Arch Intern Med.* Oct 23 2000;160(19):2926-2932.
14. Rodger M, Bredeson C, Wells PS, Beck J, Kearns B, Huebsch LB. Cost-effectiveness of low-molecular-weight heparin and unfractionated heparin in treatment of deep vein thrombosis. *CMAJ.* Oct 20 1998;159(8):931-938.
15. van den Belt AG, Bossuyt PM, Prins MH, Gallus AS, Buller HR. Replacing inpatient care by outpatient care in

the treatment of deep venous thrombosis--an economic evaluation. TASMAN Study Group. *Thromb Haemost.* Feb 1998;79(2):259-263.

16. Salih A, Hosny G. Impact of an out-patient based strategy for the management of acute deep venous thrombosis in Saudi Arabia. *European Journal of Internal Medicine.* October 2013;24:e170.
17. Otero R, Uresandi F, Jimenez D, et al. Home treatment in pulmonary embolism. *Thromb Res.* Jul 2010;126(1):e1-5.
18. Aujesky D, Roy PM, Verschuren F, et al. Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomised, non-inferiority trial. *Lancet.* Jul 2 2011;378(9785):41-48.
19. Piran S, Le Gal G, Wells PS, et al. Outpatient treatment of symptomatic pulmonary embolism: a systematic review and meta-analysis. *Thrombosis research.* Nov 2013;132(5):515-519.
20. Akl EA, Gunukula S, Barba M, et al. Parenteral anticoagulation in patients with cancer who have no therapeutic or prophylactic indication for anticoagulation. *The Cochrane database of systematic reviews.* 2011(4):CD006652.
21. Agnelli G, George DJ, Kakkar AK, et al. Semuloparin for thromboprophylaxis in patients receiving chemotherapy for cancer. *The New England journal of medicine.* Feb 16 2012;366(7):601-609.
22. Maraveyas A, Waters J, Roy R, et al. Gemcitabine versus gemcitabine plus dalteparin thromboprophylaxis in pancreatic cancer. *European journal of cancer.* Jun 2012;48(9):1283-1292.
23. van Doormaal FF, Di Nisio M, Otten HM, Richel DJ, Prins M, Buller HR. Randomized trial of the effect of the low molecular weight heparin nadroparin on survival in patients with cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* May 20 2011;29(15):2071-2076.
24. Akl EA, Vasireddi SR, Gunukula S, et al. Oral anticoagulation in patients with cancer who have no therapeutic or prophylactic indication for anticoagulation. *The Cochrane database of systematic reviews.* 2011(6):CD006466.
25. Akl EA, Vasireddi SR, Gunukula S, et al. Anticoagulation for patients with cancer and central venous catheters. *The Cochrane database of systematic reviews.* 2011(4):CD006468.
26. Lavau-Denes S, Lacroix P, Maubon A, et al. Prophylaxis of catheter-related deep vein thrombosis in cancer patients with low-dose warfarin, low molecular weight heparin, or control: a randomized, controlled, phase III study. *Cancer chemotherapy and pharmacology.* Jul 2013;72(1):65-73.
27. Akl EA, Vasireddi SR, Gunukula S, et al. Anticoagulation for the initial treatment of venous thromboembolism in patients with cancer. *The Cochrane database of systematic reviews.* 2011(6):CD006649.
28. Akl EA, Labedi N, Barba M, et al. Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer. *The Cochrane database of systematic reviews.* 2011(6):CD006650.
29. van Doormaal FF, Cohen AT, Davidson BL, et al. Idraparinux versus standard therapy in the treatment of deep venous thrombosis in cancer patients: a subgroup analysis of the Van Gogh DVT trial. *Thrombosis and haemostasis.* Jul 2010;104(1):86-91.
30. Levine MN, Gu C, Liebman HA, et al. A randomized phase II trial of apixaban for the prevention of thromboembolism in patients with metastatic cancer. *Journal of*

*thrombosis and haemostasis : JTH.* May 2012;10(5):807-814.

31. Deitcher SR, Kessler CM, Merli G, Rigas JR, Lyons RM, Fareed J. Secondary prevention of venous thromboembolic events in patients with active cancer: enoxaparin alone versus initial enoxaparin followed by warfarin for a 180-day period. *Clin Appl Thromb Hemost.* Oct 2006;12(4):389-396.
32. Hull RD, Pineo GF, Brant RF, et al. Self-managed long-term low-molecular-weight heparin therapy: the balance of benefits and harms. *Am.J.Med.* 2007;120(1):72-82.
33. Hull RD, Pineo GF, Brant R, et al. Home therapy of venous thrombosis with long-term LMWH versus usual care: patient satisfaction and post-thrombotic syndrome. *Am J Med.* Aug 2009;122(8):762-769 e763.
34. Lee AY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N.Engl.J Med.* 2003;349(2):146-153.
35. Lopaciuk S, Bielska-Falda H, Noszczyk W, et al. Low molecular weight heparin versus acenocoumarol in the secondary prophylaxis of deep vein thrombosis. *Thrombosis and Haemostasis.* 1999;81:26-31.
36. Lopez-Beret P, Orgaz A, Fontcuberta J, et al. Low molecular weight heparin versus oral anticoagulants in the long-term treatment of deep venous thrombosis. *J Vasc.Surg.* 2001;33(1):77-90.
37. Meyer G, Marjanovic Z, Valcke J, et al. Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study. *Archives of Internal Medicine.* 2002;162(15):1729-1735.
38. Romera A, Cairols MA, Vila-Coll R, et al. A randomised open-label trial comparing long-term sub-cutaneous low-molecular-weight heparin compared with oral-anticoagulant therapy in the treatment of deep venous thrombosis. *Eur J Vasc Endovasc Surg.* Mar 2009;37(3):349-356.
39. Hull RD, Pineo GF, Brant RF, et al. Long-term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer. *Am.J.Med.* 2006;119(12):1062-1072.
40. Pini M, Aiello S, Manotti C, et al. Low molecular weight heparin versus warfarin the prevention of recurrence after deep vein thrombosis. *Thrombosis and Haemostasis.* 1994;72(2):191-197.
41. Das SK, Cohen AT, Edmondson RA, Melissari E, Kakkar VV. Low-molecular-weight heparin versus warfarin for prevention of recurrent venous thromboembolism: A randomized trial. *World J.Surg.* 1996;20:521-527.
42. Gonzalez-Fajardo JA, Arreba E, Castrodeza J, et al. Venographic comparison of subcutaneous low-molecular weight heparin with oral anticoagulant therapy in the long-term treatment of deep venous thrombosis. *J Vasc.Surg.* 1999;30(2):283-292.
43. Veiga F, Escriba A, Maluenda MP, et al. Low molecular weight heparin (enoxaparin) versus oral anticoagulant therapy (acenocoumarol) in the long-term treatment of deep venous thrombosis in the elderly: a randomized trial. *Thromb.Haemost.* 2000;84(4):559-564.
44. Kakkar V, Gebska M, Kadziola Z, Saba N, Carrasco P. Low-molecular-weight heparin in the acute and long-term treatment of deep vein thrombosis. *Thrombosis and Haemostasis.* 2003;89(4):674-680.

# Appendices

1. Evidence-to-Recommendation and Summary of Findings Tables
2. Search Strategies and Results

## Appendix 1: Evidence-to-Recommendation and Summary of Findings Tables

**Evidence to recommendation framework**

***Guideline Question 1:*** *Should home treatment vs. hospital treatment be used for patients with acute DVT of the leg?*

***Panelists in attendance:*** *Dr. Almomen, Dr. Owaidah, Dr. Al Zahrani, Dr. Alsaleh, Dr. Alsheef, Dr. Algahtani*

***Additional COI declared at the beginning of the meeting:*** *none declared*

***Population:*** Patients with acute DVT of the leg
***Intervention:*** Home treatment
***Comparison:*** Hospital treatment
***Setting:*** KSA
***Perspective:*** clinical or health system

***Background and Objective:*** Published evidence suggests that home treatment is not associated with an increase in mortality, recurrent VTE or major bleeding, and may be associated with improved outcomes. It is more convenient to patients and likely to be cost effective. The guideline will address this question in the KSA healthcare setting.

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | KSA GUIDELINE PANEL CONSIDERATIONS |
|---|---|---|---|---|
| PROBLEM | **Is the problem a priority?** | *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ *Varies* ☐ | ***The baseline risks for the main outcomes of interest:*** | Do you think ***the baseline risk for any the outcomes of interest*** for the KSA guideline should be different? If yes, please provide your suggestions in the space provided in the table. Also provide citation, or at least a justification. ***Answer:*** **- No population based studies exist - A registry of 12 years from one centre exists. However, it is not representative of other centres as it includes higher risk patients.** **Is this a priority problem: - Significant number of cases seen in practice and high percentage of these cases admitted** |

| Outcome | Assumed Baseline Risk in Systematic Review | Baseline risk suggested for KSA (if thought to be different) |
|---|---|---|
| Mortality (6 months) | 46 per 1000 | - |
| Recurrent VTE (6 months) | 76 per 1000 | - |
| Major bleeding (6 months) | 21 per 1000 | - |
| Quality of life | Not available | - |

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | KSA GUIDELINE PANEL CONSIDERATIONS |
|---|---|---|---|---|
| BENEFITS & HARMS OF THE OPTIONS | **What is the overall quality of evidence?** | No included studies ☐ \| Very low ☐ \| Low ☐ \| Moderate ☒ \| High ☐ | ***The rating of the importance of the main outcomes of interest:*** | Do you think the ***rating of the importance of the main outcomes of interest*** for the KSA guideline should be different? If yes, please provide your suggestions in the space provided in the table. Also provide citation, or at least a justification. Answer: **No** |
| | **Is there important uncertainty about how much people value the main outcomes?** | Important uncertainty or variability ☐ \| Possibly important uncertainty or variability ☐ \| Probably no important uncertainty or variability ☒ \| No important uncertainty or variability ☐ \| No known undesirable outcomes ☐ | | Do you think the ***values and preferences*** for the KSA guideline should be different? Please consider how would KSA patients accpet the intervention, how important they would find the differnet outcomes of interest, etc. If yes, please provide your suggestions in the space provided in the table. Also provide citation, or at least a justification. Answer: **- Some patients and carers would prefer for the patient to be admitted** **- They may prefer to be discharged if** |
| | **Are the desirable anticipated effects large?** | No ☐ \| Probably No ☐ \| Uncertain ☐ \| Probably Yes ☒ \| Yes ☐ \| ***Varies*** ☐ | ***Summary of the evidence for patients' values and preferences:*** The panel considered from the evidence that most patients attached a relatively strong preference for being managed as outpatient versus being admitted. | |
| | **Are the undesirable anticipated effects small?** | No ☐ \| Probably No ☐ \| Uncertain ☐ \| Probably Yes ☒ \| Yes ☐ \| ***Varies*** ☐ | ***Summary of the relative effect of interventions (on both desir-*** | |

| Outcome | Relative importance |
|---|---|
| *Mortality* | Important |
| *Recurrent VTE* | Critical |
| *Major bleeding* | Critical |
| *Quality of life* | Important |

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | KSA GUIDELINE PANEL CONSIDERATIONS |
|---|---|---|---|---|
| | **Are the desirable effects large relative to undesirable effects?** | *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ ***Varies*** ☐ | ***able and undesirable outcomes) and quality of evidence*:** Please see summary of findings and references | **they know they could easily access a physician**<br><br>Are you aware of ***any relevant studies*** that are not included in the summary of findings? Answer: **No** |

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | KSA GUIDELINE PANEL CONSIDERATIONS |
|---|---|---|---|---|
| RESOURCE USE | Are the resources required small? | No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐ | ***Summary of the resource use evidence***<br>Health economic evaluations that have assessed initial treatment of DVT at home, although they have weaknesses (e.g., industry funded, not derived from trials in which LMWH was used both in hospital and at home, short time horizon (i.e., 3 months or less), and limited use of sensitivity analyses), all conclude that home treatment is cost-saving (about US$500 to US$2500 per patient).[9-15] | **Algahtani 2013:[8]**<br>**• Prospective study of 61 DVT cases presenting to ED (Aug 2009-Aug 2010) (KKUH)**<br>**• Mean outpatient cost was significantly lower ($1750 vs. $4338).**<br><br>**Aleissi 2013:[16]**<br>**• Retrospective chart analysis of DVT cases between 2005 and 2012 (KAMC)**<br>**• Of 190 DVT patients, 80 (42%) were eligible for outpatient management. Average length of stay was 7.88 days. 78.75 bed days would have been saved per year. Cost savings would be SR 118,125 per year.** |
| | Is the incremental cost small relative to the net benefits? | No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐ | | |
| EQUITY | What would be the impact on health inequities? | Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☒ Reduced ☐ Varies ☐ | No evidence identified | Based on your observations what would be the impact on ***health inequity*** if intervention were to be recommended (e.g. would health inequities be increased or reduced)? Answer:<br>**- Through the system saving beds** |
| ACCEPTABILITY | Is the option acceptable to key stakeholders? | No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐ | No evidence identified | Based on your observations what would be the ***acceptability*** of the intervention to be recommended (e.g. would the intervention be acceptable to stakeholders)? Answer:<br>**- Acceptable to physicians and Ministry of Health** |

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | KSA GUIDELINE PANEL CONSIDERATIONS |
|---|---|---|---|---|
| FEASIBILITY | **Is the option feasible to implement?** | *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ \| ***Varies*** ☐ | No evidence identified | Based on your observations what would be the ***feasibility*** of the intervention to be recommended (e.g. would the intervention be acceptable to stakeholders)? Answer:<br>**-Potentially feasible but requires 24-hour clinic coverage for these patients**<br>**-There is a lack of ultrasound service after 4:30pm and weekend in emergency rooms** |

| | | | | | |
|---|---|---|---|---|---|
| **Balance of consequences** | Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐ | Undesirable consequences *probably outweigh* desirable consequences in most settings ☐ | The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐ | Desirable consequences *probably outweigh* undesirable consequences in most settings ☒ | Desirable consequences *clearly outweigh* undesirable consequences in most settings ☐ |

| | | | | |
|---|---|---|---|---|
| **Type of recommendation** | We recommend against offering this option ☐ | We suggest not offering this option ☐ | We suggest offering this option ☒ | We recommend offering this option ☐ |

**Recommendation (text)**

For patients with simple acute DVT of the leg, the KSA MoH guideline panel suggests home treatment over hospital treatment (conditional recommendation; moderate quality evidence)

Remarks:

- Ensure that patients have support from family, access to a phone, access to a physician, and the ability to get to a hospital in a reasonable time if needed
- Consider patient level of education, knowledge about the disease, and likelihood of compliance
- Consider hospital treatment for patients with severe acute DVT of the leg and patients who are apprehensive
- This recommendation applies to anticoagulation treatment with LMWH but not NOACs

| | |
|---|---|
| **Justification** | This recommendation is conditional due to some variability in values and preferences and need to have in place 24-hour clinic coverage for these patients (e.g. thrombosis services) |
| **Subgroup considerations** | This recommendation applies to patients with simple DVT but not to patients with severe DVT |
| **Implementation considerations** | Need to make ultrasound services to assess DVT diagnosis available after 4:30pm and during weekends<br>Need to have in place 24-hour clinic coverage for these patients (e.g. thrombosis services) |
| **Monitoring and evaluation** | Evaluate the impact of implementation on outcomes and costs<br>Percentage of patients treated at home versus hospital |
| **Research priorities** | Determine local rates of events (recurrent VTE, major bleeding)<br>Assess effects of home treatment versus hospital treatment on post thrombotic syndrome |

**Summary of Findings (SoF) Table:** Home treatment compared to hospital treatment for patients with DVT

**Home treatment compared to hospital treatment for patients with DVT**

**Patient or population:** patients with patients with DVT[1,2]
**Settings:**
**Intervention:** home treatment[3,4]
**Comparison:** hospital treatment
**Bibliography:** Othieno R, Aby A, Okpo E. Home versus inpatient treatment for DVT. Cochrane database of Systematic Reviews 2007 Issue 3. Algahtani 2013

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk **Hospital treatment** | Corresponding risk **Home treatment** | | | | |
| **Mortality** | **46 per 1000** | **33 per 1000** (21 to 53) | **RR 0.72** (0.45 to 1.15) | 1708 (6 studies) | ⊕⊕⊖⊖ **low**[3,4,5,6] | |
| **Recurrent VTE** | **76 per 1000** | **49 per 1000** (33 to 71) | **RR 0.65** (0.44 to 0.94) | 1769 (7 studies) | ⊕⊕⊕⊖ **moderate**[3,4,5] | |
| **Major bleeding** | **21 per 1000** | **14 per 1000** (7 to 29) | **RR 0.67** (0.33 to 1.36) | 1708 (6 studies) | ⊕⊕⊖⊖ **low**[3,4,5,6] | |
| **Quality of life** | - | - | - | 0 (3 studies[7]) | ⊕⊕⊖⊖ **low**[8,9,10] | |
| **Post thrombotic syndrome** - not reported | - | - | - | - | - | |

*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% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] RCTs included recruited patients "whose home circumstances were adequate"
[2] RCTs included patients with leg DVT. They excluded those with PE and pregnant women
[3] 4 RCTs had partial hospital treatment for some participants in the home group: Levine 1996 (mean hospital stay 2.1 vs. 6.5 days in home and hospital arms respectively), Koopman 1996 (2.7 vs. 8.1 days), Boccalon 2000 (1 vs. 9.6 days), and Ramacciotti 2004 (3 vs. 7 days). Chong 2005 and Daskalopoulos 2005 did not report mean duration of hospital stay.
[4] One RCT (Baccalon 2000) used LMWH in both treatment groups. Remaining studies used LMWH in the outpatient group and UFH in the inpatient group.
[5] Of 7 RCTs, allocation was clearly concealed in 3 (unclear in 4), outcome adjudicators were clearly blinded in the 2 largest RCTs (unclear in remaining 5), missing data was significant in one small RCT, and analysis was ITT in 4 (unclear in remaining 3). These limitations did not warrant downgrading of quality of evidence, particularly because it had already been downgraded by at least one level for other reasons.
[6] CI includes values suggesting benefit and values suggesting harm
[7] Backman 2004, using EQ 5D, found no differences in mean QoL scores or in proportion of participants showing improvement in self-rated health state. Koopman 1996, using the Medical Outcome Study Short Form–20 and an adapted version of the Rotterdam Symptom Checklist, found that changes over time were similar in both arms (exception: had better scores for physical activity (P=0.002) and social functioning (P=0.001) in those receiving LMWH at the end of the initial treatment. O'Brien 1999, using SF-36 in 300 participants from Levine 1996, found no significant differ-

ences between the treatment arms for 7 of the 8 domains (exception: greater improvement in domain of social functioning with the outpatient group).
[8] Koopman 1996 and O'Brien 1999 showed potential benefit while Backman 2004 showed no effect, suggesting potential inconsistency
[9] 2 of 3 trials (Koopman 1996, Levine 1996) had partial hospital treatment of many in the home arm.
[10] Unable to evaluate imprecision; however it is possible. Considered along the potential inconsistency, we downgraded by one level the quality of evidence

**SoF References:**

1. Backman, K., et al., *Deep venous thrombosis: a new task for primary health care. A randomised economic study of outpatient and inpatient treatment.* Scand J Prim Health Care, 2004. 22(1): p. 44-9.
2. O'Brien, B., et al., *Economic evaluation of outpatient treatment with low-molecular-weight heparin for proximal vein thrombosis.* Arch Intern Med, 1999. 159(19): p. 2298-304.
3. Huse, D.M., et al., *Outpatient treatment of venous thromboembolism with low-molecular-weight heparin: an economic evaluation.* Am J Manag Care, 2002. 8(1 Suppl): p. S10-6.
4. Spyropoulos, A.C., et al., *Management of acute proximal deep vein thrombosis: pharmacoeconomic evaluation of outpatient treatment with enoxaparin vs inpatient treatment with unfractionated heparin.* Chest, 2002. 122(1): p. 108-14.
5. Tillman, D.J., S.L. Charland, and D.M. Witt, *Effectiveness and economic impact associated with a program for outpatient management of acute deep vein thrombosis in a group model health maintenance organization.* Arch Intern Med, 2000. 160(19): p. 2926-32.
6. Rodger, M., et al., *Cost-effectiveness of low-molecular-weight heparin and unfractionated heparin in treatment of deep vein thrombosis.* CMAJ, 1998. 159(8): p. 931-8.
7. van den Belt, A.G., et al., *Replacing inpatient care by outpatient care in the treatment of deep venous thrombosis--an economic evaluation. TASMAN Study Group.* Thromb Haemost, 1998. 79(2): p. 259-63.
8. Algahtani, F., et al., *Hospital versus home treatment of deep vein thrombosis in a tertiary care hospital in Saudi Arabia: Are we ready?* Saudi Pharm J, 2013. 21(2): p. 165-8.
9. Salih, A. and G. Hosny, *Impact of an out-patient based strategy for the management of acute deep venous thrombosis in Saudi Arabia.* European Journal of Internal Medicine, 2013. 24: p. e170.

Evidence to recommendation framework

***Guideline Question 2:*** *Should early discharge vs. standard discharge be used for patients with acute PE?*

***Panelists in attendance:*** *Dr. Alsaleh, Dr. Almomen, Dr. Owaidah, Dr. Al Zahrani*

***Additional COI declared at the beginning of the meeting:*** *none declared*

***Population:*** Patients with acute PE
***Intervention:*** Early discharge
***Comparison:*** Standard discharge
***Setting:*** KSA
***Perspective:*** clinical or health system

***Background and Objective:*** Published evidence suggests that home treatment is not associated with an increase in mortality, recurrent VTE or major bleeding, and may be associated with improved outcomes. It is more convenient to patients and likely to be cost effective. The guideline will address this question in the KSA healthcare setting.

**Definitions:**

1. Standard discharge refers to discharge as soon as the patient is clinically stable AND the parenteral anticoagulation has been discontinued (typically 1 to 3 days)
2. Early discharge refers to discharge as soon as the patient is clinically stable irrespective of whether the parenteral anticoagulation is ongoing (typically 5-7 days)

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | KSA GUIDELINE PANEL CONSIDERATIONS |
|---|---|---|---|---|
| PROBLEM | **Is the problem a priority?** | *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ *Varies* ☐ | ***The baseline risks for the main outcomes of interest:*** | Do you think ***the baseline risk for any the outcomes of interest*** for the KSA guideline should be different? If yes, please provide your suggestions in the space provided in the table. Also provide citation, or at least a justification. ***Answer:*** **- No population based studies exist** |

| Outcome | Assumed Baseline Risk in Systematic Review | Baseline risk suggested for KSA (if thought to be different) |
|---|---|---|
| Mortality (3 months) | 26 per 1000 | - |
| Non-fatal recurrent VTE (3 months) | 9 per 1000 | - |
| Major bleeding (3 months) | 4 per 1000 | - |
| Quality of life | Not available | - |

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | KSA GUIDELINE PANEL CONSIDERATIONS |
|---|---|---|---|---|
| BENEFITS & HARMS OF THE OPTIONS | **What is the overall quality of evidence?** | *No included studies* ☐ \| *Very low* ☐ \| *Low* ☐ \| *Moderate* ☒ \| *High* ☐ | ***The rating of the importance of the main outcomes of interest:*** | Do you think the ***rating of the importance of the main outcomes of interest*** for the KSA guideline should be different? If yes, please provide your suggestions in the space provided in the table. Also provide citation, or at least a justification**. Answer: No** |
| | **Is there important uncertainty about how much people value the main outcomes?** | *Important uncertainty or variability* ☐ \| *Possibly important uncertainty or variability* ☐ \| *Probably no important uncertainty or variability* ☒ \| *No important uncertainty or variability* ☐ \| *No known undesirable outcomes* ☐ | | |
| | **Are the desirable anticipated effects large?** | *No* ☐ \| *Probably No* ☐ \| *Uncertain* ☒ \| *Probably Yes* ☐ \| *Yes* ☐ \| ***Varies*** ☐ | | |
| | **Are the undesirable anticipated effects small?** | *No* ☐ \| *Probably No* ☐ \| *Uncertain* ☐ \| *Probably Yes* ☒ \| *Yes* ☐ \| ***Varies*** ☐ | | |

| Outcome | Relative importance |
|---|---|
| *Mortality* | Critical |
| *Non-fatal recurrent VTE* | Critical |
| *Major bleeding* | Critical |
| *Quality of life* | Important |

***Summary of the evidence for patients' values and preferences:***

The panel considered from the evidence that most patients who prefer the security of the hospital to the convenience and comfort of home are likely to choose hospitalization rather than home treatment.

***Summary of the relative effect of interventions (on both desirable***

Do you think the ***values and preferences*** for the KSA guideline should be different? Please consider how would KSA patients accpet the intervention, how important they would find the differnet outcomes of interest, etc.
If yes, please provide your suggestions in the space provided in the table. Also provide citation, or at least a justification.
**Answer:**
**Some patients might be more anxious than others about being discharged early**

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | KSA GUIDELINE PANEL CONSIDERATIONS |
|---|---|---|---|---|
| | **Are the desirable effects large relative to undesirable effects?** | *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ ***Varies*** ☐ | ***and undesirable outcomes) and quality of evidence*:** Please see summary of findings and references | Are you aware of ***any relevant studies*** that are not included in the summary of findings? **Answer: No** |

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | KSA GUIDELINE PANEL CONSIDERATIONS |
|---|---|---|---|---|
| RESOURCE USE | Are the resources required small? | No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ Yes ☐ Varies ☐ | No direct evidence identified<br>Probably yes due to indirect evidence | **Indirect evidence from 2 studies of DVT treatment at home:**<br>**Algahtani 2013:[8]**<br>**• Prospective study of 61 DVT cases presenting to ED (Aug 2009-Aug 2010) (KKUH)**<br>**• Mean outpatient cost was significantly lower ($1750 vs. $4338).**<br>**Aleissi 2013:[16]**<br>**• Retrospective chart analysis of DVT cases between 2005 and 2012 (KAMC)**<br>**• Of 190 DVT patients, 80 (42%) were eligible for outpatient management.**<br>**Average length of stay was 7.88 days. 78.75 bed days would have been saved per year. Cost savings would be SR 118,125 per year.** |
| | Is the incremental cost small relative to the net benefits? | No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ Yes ☐ Varies ☐ | | |
| EQUITY | What would be the impact on health inequities? | Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☒ Reduced ☐ Varies ☐ | No evidence identified | Based on your observations what would be the impact on ***health inequity*** if intervention were to be recommended (e.g. would health inequities be increased or reduced)? **Answer: probably reduced due to health expenditures savings** |

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | KSA GUIDELINE PANEL CONSIDERATIONS |
|---|---|---|---|---|
| ACCEPTABILITY | **Is the option acceptable to key stakeholders?** | *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ ***Varies*** ☐ | No evidence identified | Based on your observations what would be the ***acceptability*** of the intervention to be recommended (e.g. would the intervention be acceptable to stakeholders)? **Answer:** **Might vary by physician (apprehension to releasing patients early given the gravity of the condition)** |
| FEASIBILITY | **Is the option feasible to implement?** | *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐ | No evidence identified | Based on your observations what would be the ***feasibility*** of the intervention to be recommended (e.g. would the intervention be acceptable to stakeholders)? **Answer:** **- Potentially feasible but requires 24-hour clinic coverage for these patients** |

| **Balance of consequences** | Undesirable consequences *clearly outweigh* desirable consequences in most settings | Undesirable consequences *probably outweigh* desirable consequences in most settings | The balance between desirable and undesirable consequences *is closely balanced or uncertain* | Desirable consequences *probably outweigh* undesirable consequences in most settings | Desirable consequences *clearly outweigh* undesirable consequences in most settings |
|---|---|---|---|---|---|
| | ☐ | ☐ | ☐ | ☒ | ☐ |

| Type of recommendation | We recommend against offering this option | We suggest not offering this option | We suggest offering this option | We recommend offering this option |
|---|---|---|---|---|
| | ☐ | ☐ | ☒ | ☐ |

| | |
|---|---|
| **Recommendation (text)** | For patients with low risk acute PE, the KSA MoH guideline panel suggests early discharge over late discharge (conditional recommendation; moderate quality evidence)<br>Key considerations:<br>• Use a validated prediction rule (e.g. Pulmonary Embolism Severity Index) to risk stratify patients<br>• Ensure that patients have a close follow-up appointment<br>• Ensure that patients have support from family, access to a phone, access to a physician, and the ability to get to a hospital in a reasonable time if needed<br>• Consider patient level of education, knowledge about the disease, and likelihood of compliance<br>• Consider hospital treatment for patients with severe acute DVT of the leg and patients who are apprehensive<br>• This recommendation applies to anticoagulation treatment with LMWH but not NOACs |
| **Justification** | This recommendation is conditional due to some variability in values and preferences and need to have in place 24-hour clinic coverage for these patients (e.g. thrombosis services) |
| **Subgroup considerations** | This recommendation applies to patients with low risk PE but not to patients with higher risk PE |
| **Implementation considerations** | Need to have in place 24-hour clinic coverage for these patients (e.g. thrombosis services) |
| **Monitoring and evaluation** | Evaluate the impact of implementation on outcomes and costs<br>Percentage of patients discharged early versus late |
| **Research priorities** | Determine local rates of events (recurrent VTE, major bleeding)<br>Assess effects of early discharge on chronic thromboembolic disease, pulmonary hypertension |

**Summary of Findings (SoF) Table:** Early discharge versus standard discharge in the treatment of acute PE

**Early discharge compared to standard discharge for patients with PE**

**Patient or population:** patients with patients with PE[1]
**Settings:**
**Intervention:** early discharge[2,3]
**Comparison:** standard discharge
**Bibliography:** Otero et al [17], Aujesky et al[18], Piran 2013 [19]

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Risk with Standard discharge | Risk difference with Early discharge (95% CI) | | | | |
| **Mortality**<br>Follow-up: 3 months | **26 per 1000** | **11 fewer per 1000**<br>(from 22 fewer to 26 more) | **RR 0.58**<br>(0.17 to 1.97) | 471<br>(2 studies) | ⊕⊕⊕⊖<br>**MODERATE**[3,4]<br>due to imprecision | |
| **Non-fatal recurrent VTE**<br>Follow-up: 3 months | **9 per 1000** | **2 more per 1000**<br>(from 7 fewer to 44 more) | **RR 1.23**<br>(0.25 to 6.03) | 471<br>(2 studies) | ⊕⊕⊕⊖<br>**MODERATE**[3,4]<br>due to imprecision | |
| **Major bleeding** | **4 per 1000** | **8 more per 1000**<br>(from 2 fewer to 69 more) | **RR 2.74**<br>(0.45 to 16.71) | 471<br>(2 studies) | ⊕⊕⊕⊖<br>**MODERATE**[3,4]<br>due to imprecision | |
| **Quality of life** - not measured | - | - | Not estimable | - | - | |
| **Post thrombotic syndrome** - not measured | - | - | Not estimable | - | - | |

*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% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] The 2 trials included patients at low risk: low risk on clinical prediction rule (Uresandi 2007); risk classes I or II on the PE severity index (Aujesky 2011).
[2] Length of hospital stay: 3.4 (1.1) vs. 9.3 (5.7) in Ottero 2010 and 0.5 (1) vs. 3.9 (3.1) in Aujesky 2011; low risk on clinical prediction rule by Uresandi 2007 in Otero.
[3] Aujesky 2011: allocation concealment unclear; 3 patients (1%) with missing data; ITT; blinding of outcome adjudicators; no early stopping for benefit. Otero 2010: allocation concealed; no missing data; ITT; no blinding reported; trial stopped early as the "rate of short-term mortality was unexpectedly high" in the early discharge group: 2 (2.8%) vs. 0 (0%).
[4] CI includes values suggesting no effect and values suggesting appreciable benefit or appreciable harm.

**SoF References:**

1. Algahtani, F., et al., *Hospital versus home treatment of deep vein thrombosis in a tertiary care hospital in Saudi Arabia: Are we ready?* Saudi Pharm J, 2013. **21**(2): p. 165-8.
2. Salih, A. and G. Hosny, *Impact of an out-patient based strategy for the management of acute deep venous thrombosis in Saudi Arabia.* European Journal of Internal Medicine, 2013. **24**: p. e170.
3. Otero, R., et al., *Home treatment in pulmonary embolism.* Thromb Res, 2010. **126**(1): p. e1-5.
4. Aujesky, D., et al., *Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomised, non-inferiority trial.* Lancet, 2011. **378**(9785): p. 41-8.
5. Piran, S., et al., *Outpatient treatment of symptomatic pulmonary embolism: a systematic review and meta-analysis.* Thromb Res, 2013. **132**(5): p. 515-9.

Evidence to recommendation framework

***Guideline Question 3:*** *Should heparin vs no heparin be used in outpatients with cancer who have no other therapeutic or prophylactic indication for anticoagulation?*

***Panelists in attendance:*** *Dr. Almomen, Dr. Owaidah, Dr. Al Zahrani, Dr. Alsaleh*

***Additional COI declared at the beginning of the meeting:*** *none declared*

***Population*:** outpatients with cancer who have no other therapeutic or prophylactic indication for anticoagulation
***Intervention*:** Heparin treatment
***Comparison*:** No heparin treatment
***Setting*:** KSA
***Perspective*:** clinical or health system

***Background and Objective:*** Based on published evidence, heparin treatment in patients with cancer who have no other therapeutic or prophylactic indication for anticoagulation, can lead to likely reduction of mortality and a certain reduction of VTE with slight increase of major bleeding.

***Definition of population:*** Ambulatory cancer patients that are typically undergoing chemotherapy and/or radiotherapy, and have no typical indication for thromboprophylaxis (e.g., immobility)

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | KSA GUIDELINE PANEL CONSIDERATIONS |
|---|---|---|---|---|
| PROBLEM | **Is the problem a priority?** | *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ *Varies* ☐ | ***The baseline risks for the main outcomes of interest:*** | Do you think ***the baseline risk for any the outcomes of interest*** for the KSA guideline should be different? If yes, please provide your suggestions in the space provided in the table. Also provide citation, or at least a justification. ***Answer: no local data available*** **Priority of the problem: potential morbidity and mortality in cancer patients due to VTE. But total number of patients at risk is relatively small.** |

| Outcome | Assumed Baseline Risk in Systematic Review | Baseline risk suggested for KSA (if thought to be different) |
|---|---|---|
| Mortality (12 months) | 459 per 1000 | - |
| Symptomatic VTE (12 months) | 51 per 1000 | - |
| Major bleeding (12 months) | 16 per 1000 | - |
| Minor bleeding (12 weeks) | 28 per 1000 | - |
| Quality of life | Not available | - |

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | KSA GUIDELINE PANEL CONSIDERATIONS |
|---|---|---|---|---|
| BENEFITS & HARMS OF THE OPTIONS | **What is the overall quality of evidence?** | *No included studies* ☐ \| *Very low* ☐ \| *Low* ☐ \| *Moderate* ☒ \| *High* ☐ | ***The rating of the importance of the main outcomes of interest:*** | Do you think the ***rating of the importance of the main outcomes of interest*** for the KSA guideline should be different? If yes, please provide your suggestions in the space provided in the table. Also provide citation, or at least a justification. **Answer: No** |
| | **Is there important uncertainty about how much people value the main outcomes?** | *Important uncertainty or variability* ☐ \| *Possibly important uncertainty or variability* ☐ \| *Probably no important uncertainty or variability* ☐ \| *No important uncertainty or variability* ☒ \| *No known undesirable outcomes* ☐ | | |
| | **Are the desirable anticipated effects large?** | *No* ☐ \| *Probably No* ☒ \| *Uncertain* ☐ \| *Probably Yes* ☐ \| *Yes* ☐ \| ***Varies*** ☐ | ***Summary of the evidence for patients' values and preferences:*** | Do you think the ***values and preferences*** for the KSA guideline should be different? Please consider how would KSA patients accpet the intervention, how important they would find the differnet outcomes of interest, etc. If yes, please provide your suggestions in the space provided in the table. Also provide citation, or at least a justification. **Answer:** **Typically patients would be against daily injections for duration of several months. Patients would view potential** |
| | **Are the undesirable anticipated effects small?** | *No* ☐ \| *Probably No* ☐ \| *Uncertain* ☐ \| *Probably Yes* ☐ \| *Yes* ☒ \| ***Varies*** ☐ | ***Summary of the relative effect of interventions (on both desira-*** | |

| Outcome | Relative importance |
|---|---|
| Mortality | Critical |
| Symptomatic VTE | Critical |
| Major bleeding | Important |
| Minor bleeding | Not important |
| Quality of life | Not important |

Not explicitly reported

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | KSA GUIDELINE PANEL CONSIDERATIONS |
|---|---|---|---|---|
| | **Are the desirable effects large relative to undesirable effects?** | *No* ☐ *Probably No* ☒ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☐ ***Varies*** ☐ | ***ble and undesirable outcomes) and quality of evidence*:** Please see summary of findings and references | **reduction in mortality and symptomatic VTE favorably.**<br><br>Are you aware of ***any relevant studies*** that are not included in the summary of findings? **Answer: No**<br><br>**Note: Anticiapted desirable effects larger for patients at higher risk of adverse events** |

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | KSA GUIDELINE PANEL CONSIDERATIONS |
|---|---|---|---|---|
| RESOURCE USE | **Are the resources required small?** | No ☐ / Probably No ☒ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / **Varies** ☐ | No evidence identified | What are the annual costs directly related to the intervention and complications in the KSA setting? Please provide your best (note whether in U.S Dollars or Saudi Arabian Riyal). **Answer: Panel estimated the cost at SR 20 per injection per day (a smal unit cost). Applied to the population level for a period of 6 months for 13,000 patients: SR 46 .8 Million. 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 clinic or have nurse home visits.** |
| | **Is the incremental cost small relative to the net benefits?** | No ☐ / Probably No ☒ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / **Varies** ☐ | | |
| EQUITY | **What would be the impact on health inequities?** | Increased ☐ / Probably increased ☒ / Uncertain ☐ / Probably reduced ☐ / Reduced ☐ / **Varies** ☐ | No evidence identified | Based on your observations what would be the impact on ***health inequity*** if intervention were to be recommended (e.g. would health inequities be increased or reduced)? **Answer: this intervention would take away resources from other areas.** |

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | KSA GUIDELINE PANEL CONSIDERATIONS |
|---|---|---|---|---|
| ACCEPTABILITY | **Is the option acceptable to key stakeholders?** | *No* ☐ *Probably No* ☒ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☐ ***Varies*** ☐ | No evidence identified | Based on your observations what would be the ***acceptability*** of the intervention to be recommended (e.g. would the intervention be acceptable to stakeholders)? **Answer: it would be hard to accept by policymakers due to cost and given this is a prophylaxis intervention.** |
| FEASIBILITY | **Is the option feasible to implement?** | *No* ☐ *Probably No* ☒ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☐ ***Varies*** ☐ | No evidence identified | Based on your observations what would be the ***feasibility*** of the intervention to be recommended (e.g. would the intervention be acceptable to stakeholders)? **Answer: probably no** |

| | | | | | |
|---|---|---|---|---|---|
| **Balance of consequences** | Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐ | Undesirable consequences *probably outweigh* desirable consequences in most settings ☒ | The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐ | Desirable consequences *probably outweigh* undesirable consequences in most settings ☐ | Desirable consequences *clearly outweigh* undesirable consequences in most settings ☐ |

| | | | | |
|---|---|---|---|---|
| **Type of recommendation** | We recommend against offering this option | We suggest not offering this option | We suggest offering this option | We recommend offering this option |
| | ☐ | ☒ | ☐ | ☐ |

| | |
|---|---|
| **Recommendation (text)** | For outpatients with cancer, the KSA MoH guideline panel suggests against thromboprophylaxis with heparin (conditional recommendation; moderate quality evidence)<br>Key considerations:<br>• Use a validated tool (e.g., Khorana JNCCN 2011;9:789-798) to risk stratify patients, as those at higher risk for VTE are more likely to benefit<br>• 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). |
| **Justification** | This recommendation is conditional against due to the small absolute benefits, small harms, and large burden due to injections |
| **Subgroup considerations** | Although there is evidence for potential benefit in patients with small lung cell cancers, the evidence is of lower quality, so the recommendation applies to all types of cancers IPD-MA being conducted |
| **Implementation considerations** | - |
| **Monitoring and evaluation** | - |
| **Research priorities** | Identify which types and stages of cancer are more likely to benefit (IPDMA being conducted)<br>Assess cost effectiveness |

**Summary of Findings (SoF) table:** heparin vs no heparin be used in patients with cancer who have no other therapeutic or prophylactic indication for anti-coagulation

**LMWH compared to no LMWH for anticoagulation**

**Patient or population:** patients with anticoagulation
**Settings:**
**Intervention:** LMWH
**Comparison:** no LMWH[1]
**Bibliography:** Akl et al. Parenteral anticoagulation in patients with cancer who have no therapeutic or prophylactic indication for anticoagulation. Cochrane Database of Systematic Reviews 2013 update with 3 newly included studies.[20-23]

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk **No LMWH** | Corresponding risk **LMWH** | | | | |
| **Mortality at 12 months** Follow-up: 12 months | **459 per 1000** | **436 per 1000** (409 to 459) | **RR 0.95** (0.89 to 1) | 7266 (13 studies) | ⊕⊕⊕⊖ **moderate**[2,3,4] | The Hazard ratio, based on data from 9 studies, for the duration of follow-up is 0.83 (95% CI 0.72, 0.95). |
| **Symptomatic VTE** | **51 per 1000** | **29 per 1000** (22 to 38) | **RR 0.56** (0.43 to 0.74) | 6998 (12 studies) | ⊕⊕⊕⊕ **high** | |
| **Major bleeding** | **16 per 1000** | **18 per 1000** (13 to 26) | **RR 1.14** (0.8 to 1.63) | 7539 (14 studies) | ⊕⊕⊕⊖ **moderate**[5] | |
| **Minor bleeding** | **28 per 1000** | **31 per 1000** (25 to 44) | **RR 1.1** (0.89 to 1.55) | 7041 (12 studies) | ⊕⊕⊕⊕ **high**[6] | |

*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% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] The baseline risks are derived from the included studies in which the follow-up period was 6 to 12 months on average
[2] I2 = 15%, indicating some, but no serious heterogeneity across studies.
[3] Imprecision (and some concern about publication bias) led us to downgrade the quality of evidence to moderate given that the results are borderline statistical significant and decision makers may base their decision on the critical outcome mortality. However, it should be noted that the survival analysis and the results expressed as hazards ratios and the relative risk of death at 24 months based on 5 studies that provided data is statistically significant.
[4] Although publication bias was not detected, it remains possible that moderate size studies would influence this estimate importantly, in particular in view of the borderline statistical significance.
[5] The imprecision of the point estimate (indicated by the confidence intervals) indicates that a relative risk increase of up to 57% is still possible albeit unlikely. We downgraded for imprecision and because the absolute effects, although small, may be substantially different in settings where patients are not partaking in randomized controlled trials (indirectness). As the CIs for mortality and VTE become narrower even a 57% increase may be acceptable given that VTEs, similar to major bleeding, lead to unpleasant hospital admissions, possibly with invasive procedures.
[6] It is not clear why 2 studies did not report on minor bleeding and selective outcome reporting bias is a concern, although we did not downgrade.

**SoF References:**

1. Agnelli, G., et al., *Semuloparin for thromboprophylaxis in patients receiving chemotherapy for cancer.* N Engl J Med, 2012. 366(7): p. 601-9.
2. Akl, E.A., et al., *Parenteral anticoagulation in patients with cancer who have no therapeutic or prophylactic indication for anticoagulation.* Cochrane Database Syst Rev, 2011(4): p. CD006652.
3. Maraveyas, A., et al., *Gemcitabine versus gemcitabine plus dalteparin thromboprophylaxis in pancreatic cancer.* Eur J Cancer, 2012. 48(9): p. 1283-92.
4. van Doormaal, F.F., et al., *Randomized trial of the effect of the low molecular weight heparin nadroparin on survival in patients with cancer.* J Clin Oncol, 2011. 29(15): p. 2071-6.

Evidence to recommendation framework

***Guideline Question 4:*** *Should oral anticoagulation vs no oral anticoagulation be used in outpatients with cancer who have no other therapeutic or prophylactic indication for anticoagulation?*

***Panelists in attendance:*** *Dr. Almomen, Dr. Owaidah, Dr. Al Zahrani, Dr. Alsheef*

***Additional COI declared at the beginning of the meeting:*** *none declared*

***Population:*** outpatients with cancer who have no other therapeutic or prophylactic indication for anticoagulation
***Intervention:*** oral anticoagulation
***Comparison:*** No oral anticoagulation
***Setting:*** KSA
***Perspective:*** clinical or health system

***Background and Objective:*** Based on published evidence, oral anticoagulation in outpatients with cancer who have no other therapeutic or prophylactic indication for anticoagulation does not appear to impact mortality, or VTE and is likely to increase the risk of major bleeding.

***Definition of population:*** Ambulatory cancer patients that are typically undergoing chemotherapy and/or radiotherapy, and have no typical indication for thromboprophylaxis (e.g., immobility)

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | KSA GUIDELINE PANEL CONSIDERATIONS |
|---|---|---|---|---|
| PROBLEM | **Is the problem a priority?** | *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ ***Varies*** ☐ | ***The baseline risks for the main outcomes of interest:*** | Do you think ***the baseline risk for any the outcomes of interest*** for the KSA guideline should be different? If yes, please provide your suggestions in the space provided in the table. Also provide citation, or at least a justification. ***Answer: no local data available*** **Priority of the problem: potential morbidity and mortality in cancer patients due to VTE. But total number of patients at risk is relatively small.** |

| Outcome | Assumed Baseline Risk in Systematic Review | Baseline risk suggested for KSA (if thought to be different) |
|---|---|---|
| Mortality (1year) | 649 per 1000 | - |
| VTE (1year) | 29 per 1000 | - |
| Major bleeding (1year) | 7 per 1000 | - |
| Minor bleeding (1year) | 27 per 1000 | - |
| Quality of life (1year) | Not available | - |

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | KSA GUIDELINE PANEL CONSIDERATIONS |
|---|---|---|---|---|
| BENEFITS & HARMS OF THE OPTIONS | **What is the overall quality of evidence?** | No included studies ☐ \| Very low ☐ \| Low ☐ \| Moderate ☒ \| High ☐ | ***The rating of the importance of the main outcomes of interest:*** | Do you think the ***rating of the importance of the main outcomes of interest*** for the KSA guideline should be different? If yes, please provide your suggestions in the space provided in the table. Also provide citation, or at least a justification. **Answer: No** |
| | **Is there important uncertainty about how much people value the main outcomes?** | Important uncertainty or variability ☐ \| Possibly important uncertainty or variability ☐ \| Probably no important uncertainty or variability ☒ \| No important uncertainty or variability ☐ \| No known undesirable outcomes ☐ | **Outcome** / **Relative importance**<br>Mortality — Critical<br>Symptomatic VTE — Important<br>Major bleeding — Important<br>Minor bleeding — Not important<br>Quality of life — Important | |
| | **Are the desirable anticipated effects large?** | No ☒ \| Probably No ☐ \| Uncertain ☐ \| Probably Yes ☐ \| Yes ☐ \| ***Varies*** ☐ | ***Summary of the evidence for patients' values and preferences:***<br>Not explicitly reported | Do you think the ***values and preferences*** for the KSA guideline should be different? Please consider how would KSA patients accpet the intervention, how important they would find the differnet outcomes of interest, etc.<br>If yes, please provide your suggestions in the space provided in the table. Also provide citation, or at least a justification.<br>**Answer:** |
| | **Are the undesirable anticipated effects small?** | No ☐ \| Probably No ☒ \| Uncertain ☐ \| Probably Yes ☐ \| Yes ☐ \| ***Varies*** ☐ | ***Summary of the relative effect of interventions (on both desir-*** | **Oral anticoagulation requires frequent** |

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | KSA GUIDELINE PANEL CONSIDERATIONS |
|---|---|---|---|---|
| | **Are the desirable effects large relative to undesirable effects?** | *No* ☐ *Probably No* ☒ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☐ ***Varies*** ☐ | ***able and undesirable outcomes) and quality of evidence*:** Please see summary of findings and references | **testing and monitoring, diet and medication restrictions, stoppage for procedures, etc.**<br>**Patients would view potential reduction in mortality and symtomatic VTE favorably.**<br><br>Are you aware of ***any relevant studies*** that are not included in the summary of findings? **Answer: No** |

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | KSA GUIDELINE PANEL CONSIDERATIONS |
|---|---|---|---|---|
| RESOURCE USE | **Are the resources required small?** | *No* ☐ *Probably No* ☒ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☐ ***Varies*** ☐ | No evidence identified | What are the annual costs directly related to the intervention and complications in the KSA setting? Please provide your best (note whether in U.S Dollars or Saudi Arabian Riyal). **Answer: unit cost is low. Visits for monitoring, lab testing would require significant resources.**<br><br>Please suggest any relevant studies providing evidence about the use of resources (e.g., economic evaluations, cost-effectiveness, or resource utilization for the interventions in KSA). **Answer: None** |
| | **Is the incremental cost small relative to the net benefits?** | *No* ☒ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☐ ***Varies*** ☐ | | |
| EQUITY | **What would be the impact on health inequities?** | *Increased* ☐ *Probably increased* ☒ *Uncertain* ☐ *Probably reduced* ☐ *Reduced* ☐ ***Varies*** ☐ | No evidence identified | Based on your observations what would be the impact on ***health inequity*** if intervention were to be recommended (e.g. would health inequities be increased or reduced)? Answer: |
| ACCEPTABILITY | **Is the option acceptable to key stakeholders?** | *No* ☐ *Probably No* ☒ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☐ ***Varies*** ☐ | No evidence identified | Based on your observations what would be the ***acceptability*** of the intervention to be recommended (e.g. would the intervention be acceptable to stakeholders)? **Answer: probably not because not effective (no effect on mortality) and not cost-effective for prevention.** |

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | KSA GUIDELINE PANEL CONSIDERATIONS |
|---|---|---|---|---|
| FEASIBILITY | **Is the option feasible to implement?** | *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ ***Varies*** ☐ | No evidence identified | Based on your observations what would be the ***feasibility*** of the intervention to be recommended (e.g. would the intervention be acceptable to stakeholders)? **Answer: more feasible than heparin.** |

| | | | | | |
|---|---|---|---|---|---|
| **Balance of consequences** | Undesirable consequences *clearly outweigh* desirable consequences in most settings ☒ | Undesirable consequences *probably outweigh* desirable consequences in most settings ☐ | The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐ | Desirable consequences *probably outweigh* undesirable consequences in most settings ☐ | Desirable consequences *clearly outweigh* undesirable consequences in most settings ☐ |

| | | | | |
|---|---|---|---|---|
| **Type of recommendation** | We recommend against offering this option ☒ | We suggest not offering this option ☐ | We suggest offering this option ☐ | We recommend offering this option ☐ |

| | |
|---|---|
| **Recommendation (text)** | For outpatients with cancer, the KSA MoH guideline panel recommends against thromboprophylaxis with oral anticoagulation (strong recommendation; moderate quality evidence)<br>Key consideration<br>• 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). |
| **Justification** | The recommendation is against due to the lack of mortality benefit and closely balanced (uncertain) reduction in VTE and increased in bleeding |
| **Subgroup considerations** | The recommendation applies to all types and stages of cancers |
| **Implementation considerations** | - |
| **Monitoring and evaluation** | - |
| **Research priorities** | Conduct studies in high-risk patients<br>Conduct studies to test new oral anticoagulants. |

**Summary of Findings (SoF) table:** oral anticoagulation vs no oral anticoagulation be used in patients with cancer who have no other therapeutic or prophylactic indication for anticoagulation

**Oral anticoagulation in patients with cancer with no therapeutic or prophylactic indication for anticoagulation**

**Patient or population:** patients with cancer with no therapeutic or prophylactic indication for anticoagulation.
**Settings:** Outpatient
**Intervention:** oral anticoagulation[1]

**Bibliography:** Akl et al. Oral anticoagulation for prolonging survival in patients with cancer. Cochrane Database of Systematic Reviews. 2013 update identified one new trial [24,30]

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk **Control** | Corresponding risk **Oral anticoagulation** | | | | |
| **Death** Follow-up: median 1 years | **Moderate**[2] | | **RR 0.94** (0.87 to 1.03) | 1604 (5 studies) | ⊕⊕⊕⊖ **moderate**[3] | |
| | **649 per 1000** | **610 per 1000** (565 to 668) | | | | |
| **Symptomatic VTE** Follow-up: 1 years | **Moderate**[2] | | **RR 0.15** (0.02 to 1.2) | 315 (1 study) | ⊕⊕⊕⊖ **moderate**[4] | |
| | **29 per 1000** | **4 per 1000** (1 to 35) | | | | |
| **Major bleeding** Follow-up: median 1 years | **Moderate**[2] | | **RR 4.24** (1.85 to 9.68) | 1282 (4 studies) | ⊕⊕⊕⊖ **moderate**[5] | |
| | **7 per 1000** | **30 per 1000** (13 to 68) | | | | |
| **Minor bleeding** Follow-up: 1 years | **Moderate**[2] | | **RR 3.34** (1.66 to 6.74) | 851 (3 studies) | ⊕⊕⊕⊖ **moderate**[5] | |
| | **27 per 1000** | **90 per 1000** (45 to 182) | | | | |
| **Health related quality of life** - not reported | See comment | See comment | Not estimable | - | See comment | |

*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% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] All studies used warfarin at a dose to increase prothrombin time (PT) 1.5 to 2 times (4 studies) or to keep INR between 1.3 and 1.9.
[2] Baseline risk is the median of risk in control groups of trials included in a systematic review of the effects of parenteral anticoagulation in patients with cancer but no prophylactic or therapeutic indication for anticoagulation (Akl et al. Cochrane Database of Systematic Reviews. 2011)

[3] Quality of evidence downgraded due to lack of blinding of participants and providers in 4 out of 5 trials; unclear whether allocation concealed in 2 trials; only one study reported using intention to treat analysis.
[4] Quality of evidence downgraded due to the imprecision (lower limit of RR suggests a benefit that might be considered clinically significant given the high baseline risk).
[5] Quality of evidence downgraded due to lack of blinding of participants and providers in 3 out of 4 trials; unclear whether allocation concealed in 2 trials; only one study reported using intention to treat analysis.

**NB:** one new study identified (Levine J Thromb Haemost 2012; 10: 807–14) compared apixaban vs. no apixaban; the study did not assess mortality at 12 months; including the study in the meta-analysis of mortality at 12 months did not substantively affect the results (RR 0.92 [0.70, 1.20])

## SoF References:

1. Akl, E.A., et al., *Oral anticoagulation in patients with cancer who have no therapeutic or prophylactic indication for anticoagulation.* Cochrane Database Syst Rev, 2011(6): p. CD006466.
2. Levine, M.N., et al., *A randomized phase II trial of apixaban for the prevention of thromboembolism in patients with metastatic cancer.* J Thromb Haemost, 2012. **10**(5): p. 807-14.

Evidence to recommendation framework

***Guideline Question 5:*** *Should parenteral anticoagulation vs no anticoagulation be used in patients with cancer and central venous catheters?*

***Panelists in attendance:*** *Dr. Owaidah, Dr. Al Zahrani, Dr. Algahtani, Dr. Alsheef*

***Additional COI declared at the beginning of the meeting:*** *none declared*

***Population:*** cancer patients with central venous catheters
***Intervention:*** parenteral anticoagulation
***Comparison:*** No parenteral anticoagulation
***Setting:*** KSA
***Perspective:*** clinical or health system

***Background and Objective:*** Studies of oral anticoagulation in cancer patients with central venous catheters suggest a certain absolute risk increase of bleeding that outweighs a less certain absolute risk reduction of recurrent VTE. The effect on overall mortality is also less certain.

***Definition of population:*** Ambulatory cancer patients with CVC that are typically undergoing chemotherapy and/or radiotherapy, and have no typical indication for thromboprophylaxis (e.g., immobility)

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | KSA GUIDELINE PANEL CONSIDERATIONS |
|---|---|---|---|---|
| PROBLEM | **Is the problem a priority?** | *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ *Varies* ☐ | ***The baseline risks for the main outcomes of interest:*** | Do you think ***the baseline risk for any the outcomes of interest*** for the KSA guideline should be different? If yes, please provide your suggestions in the space provided in the table. Also provide citation, or at least a justification. ***Answer: no local data available*** **Priority of the problem: central line use is common. Patients already have cancer and dealing with chemo and thrombosis would be additional problem.** |

| Outcome | Assumed Baseline Risk in Systematic Review | Baseline risk suggested for KSA (if thought to be different) |
|---|---|---|
| Mortality (6 months) | 260 per 1000 | - |
| Symptomatic DVT (6 months) | 109 per 1000 | - |
| Major bleeding (6 months) | 2 per 1000 | - |
| Quality of life | Not available | - |

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | KSA GUIDELINE PANEL CONSIDERATIONS |
|---|---|---|---|---|
| BENEFITS & HARMS OF THE OPTIONS | **What is the overall quality of evidence?** | *No included studies* ☐ \| *Very low* ☐ \| *Low* ☐ \| *Moderate* ☒ \| *High* ☐ | ***The rating of the importance of the main outcomes of interest:*** | Do you think the ***rating of the importance of the main outcomes of interest*** for the KSA guideline should be different? If yes, please provide your suggestions in the space provided in the table. Also provide citation, or at least a justification. **Answer: No** |
| | **Is there important uncertainty about how much people value the main outcomes?** | *Important uncertainty or variability* ☐ \| *Possibly important uncertainty or variability* ☐ \| *Probably no important uncertainty or variability* ☒ \| *No important uncertainty or variability* ☐ \| *No known undesirable outcomes* ☐ | **Mortality** — **Relative importance**<br>Mortality — Critical<br>Symptomatic DVT — Critical<br>Major bleeding — Critical<br>Quality of life — Important | Do you think the ***values and preferences*** for the KSA guideline should be different? Please consider how would KSA patients accpet the intervention, how important they would find the differnet outcomes of interest, etc.<br>If yes, please provide your suggestions in the space provided in the table. Also provide citation, or at least a justification.<br>**Answer: Typically patients would be against daily injections for duration of several months. Patients would view potential reduction in mortality and symptomatic VTE favorably.** |
| | **Are the desirable anticipated effects large?** | *No* ☐ \| *Probably No* ☐ \| *Uncertain* ☐ \| *Probably Yes* ☒ \| *Yes* ☐ \| ***Varies*** ☐ | ***Summary of the evidence for patients' values and preferences:***<br>Not explicitly reported | |
| | **Are the undesirable anticipated effects small?** | *No* ☐ \| *Probably No* ☐ \| *Uncertain* ☐ \| *Probably Yes* ☐ \| *Yes* ☒ \| ***Varies*** ☐ | ***Summary of the relative effect of interventions (on both desirable and undesirable outcomes) and quality of evidence*:**<br>Please see summary of findings and references | Are you aware of ***any relevant studies*** that are not included in the summary of findings? **Answer: No** |
| | **Are the desirable effects large relative to undesirable effects?** | *No* ☐ \| *Probably No* ☐ \| *Uncertain* ☐ \| *Probably Yes* ☐ \| *Yes* ☒ \| ***Varies*** ☐ | | **Note: Larger anticiapted effects for** |

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | KSA GUIDELINE PANEL CONSIDERATIONS |
|---|---|---|---|---|
| | | | | patients at high risk for VTE |

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | KSA GUIDELINE PANEL CONSIDERATIONS |
|---|---|---|---|---|
| RESOURCE USE | **Are the resources required small?** | *No* ☐ *Probably No* ☐ *Uncertain* ☒ *Probably Yes* ☐ *Yes* ☐ ***Varies*** ☐ | No evidence identified | What are the annual costs directly related to the intervention and complications in the KSA setting? Please provide your best (note whether in U.S Dollars or Saudi Arabian Riyal). **Answer: relatively short time period (e.g. 3 months). Number of patients with CVC 20-30% of 13,000 = ~2000 patients.**<br><br>Please suggest any relevant studies providing evidence about the use of resources (e.g., economic evaluations, cost-effectiveness, or resource utilization for the interventions in KSA). **Answer: None** |
| | **Is the incremental cost small relative to the net benefits?** | *No* ☐ *Probably No* ☐ *Uncertain* ☒ *Probably Yes* ☐ *Yes* ☐ ***Varies*** ☐ | | |
| EQUITY | **What would be the impact on health inequities?** | *Increased* ☐ *Probably increased* ☐ *Uncertain* ☒ *Probably reduced* ☐ *Reduced* ☐ ***Varies*** ☐ | No evidence identified | Based on your observations what would be the impact on ***health inequity*** if intervention were to be recommended (e.g. would health inequities be increased or reduced)? **Answer: None** |

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | KSA GUIDELINE PANEL CONSIDERATIONS |
|---|---|---|---|---|
| ACCEPTABILITY | **Is the option acceptable to key stakeholders?** | *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ ***Varies*** ☐ | No evidence identified | Based on your observations what would be the ***acceptability*** of the intervention to be recommended (e.g. would the intervention be acceptable to stakeholders)? **Answer: Given it is relatively short period, more likely to be acceptable.** |
| FEASIBILITY | **Is the option feasible to implement?** | *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ ***Varies*** ☐ | No evidence identified | Based on your observations what would be the ***feasibility*** of the intervention to be recommended (e.g. would the intervention be acceptable to stakeholders)? Answer: **Patients would be coming back any way to take care of catheter** |

| **Balance of consequences** | Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐ | Undesirable consequences *probably outweigh* desirable consequences in most settings ☐ | The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☒ | Desirable consequences *probably outweigh* undesirable consequences in most settings ☐ | Desirable consequences *clearly outweigh* undesirable consequences in most settings ☐ |
|---|---|---|---|---|---|

| Type of recommendation | We recommend against offering this option | We suggest not offering this option | We suggest offering this option | We recommend offering this option |
|---|---|---|---|---|
| | ☐ | ☐ | ☒ | ☐ |

| | |
|---|---|
| **Recommendation (text)** | For outpatients with cancer and CVC, the KSA MoH guideline panel suggests thromboprophylaxis with parenteral anticoagulation (weak recommendation; moderate quality evidence)<br>Key considerations:<br>• Use a validated tool (e.g., Khorana JNCCN 2011;9:789-798) to risk stratify patients, as those at higher risk for VTE are more likely to benefit<br>• 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). |
| **Justification** | Moderate quality evidence suggests benefits |
| **Subgroup considerations** | None |
| **Implementation considerations** | - |
| **Monitoring and evaluation** | - |
| **Research priorities** | Studies comparing new oral anticoagulants vs. heparin<br>KSA cost-effectiveness studies |

**Summary of Findings (SoF) table:** parenteral anticoagulation vs no parenteral anticoagulation be used in cancer patients with central venous catheters

**Heparin compared to no heparin for thrombosis prophylaxis 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
**Bibliography:** Akl et al. Anticoagulation for thrombosis prophylaxis in cancer patients with central venous catheters. Cochrane Database of Systematic Reviews. 2013 update

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk **No heparin** | Corresponding risk **Heparin** | | | | |
| **Death** | **64 per 1000** | **54 per 1000** (35 to 83) | **RR 0.85** (0.55 to 1.31) | 1474 (6 studies) | ⊕⊕⊕⊖ **moderate**[1,2,3] | |
| **Symptomatic DVT** | **80 per 1000** | **43 per 1000** (28 to 68) | **RR 0.54** (0.35 to 0.85) | 1455 (7 studies) | ⊕⊕⊕⊕ **high**[1,2] | |
| **Major bleeding** | **5 per 1000** | **4 per 1000** (1 to 26) | **RR 0.68** (0.1 to 4.78) | 891 (4 studies) | ⊕⊕⊕⊖ **moderate**[1,2,3] | |
| **Infection** | **71 per 1000** | **65 per 1000** (35 to 120) | **RR 0.91** (0.49 to 1.68) | 626 (3 studies) | ⊕⊕⊕⊖ **moderate**[1,2] | |
| **Thrombocytopenia** | **156 per 1000** | **163 per 1000** (125 to 210) | **RR 1.04** (0.8 to 1.34) | 1118 (4 studies) | ⊕⊕⊕⊖ **moderate**[1,2,3] | |
| **Quality of life** - not reported | See comment | See comment | Not estimable | - | See comment | |

*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% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Allocation concealed in 3 of the 7 trials. 4 trials blinded participants and providers and all trials blinded outcome adjudicators. 3 trials had no problem with missing data. No suspicion of selective reporting. Three studies reported using intention to treat.
[2] Small number of events
[3] CI includes values suggesting no effect and values suggesting either harm or benefit

**Summary of Findings (SoF) table:** parenteral anticoagulation vs oral anticoagulation be used in cancer patients with central venous catheters

**LMWH compared to VKA for thrombosis prophylaxis 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
**Bibliography:** Akl et al. Anticoagulation for thrombosis prophylaxis in cancer patients with central venous catheters. Cochrane Database of Systematic Reviews. 2013 update identified one new trial [25,26]

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk **VKA** | Corresponding risk **LMWH** | | | | |
| **Death** | **87 per 1000** | **96 per 1000** (56 to 168) | **RR 1.11** (0.64 to 1.93) | 623 (3 studies) | ⊕⊕⊖⊖ **low**[1,2,3] | |
| **Symptomatic DVT** | **43 per 1000** | **67 per 1000** (33 to 137) | **RR 1.55** (0.76 to 3.15) | 560 (3 studies) | ⊕⊕⊖⊖ **low**[1,2,3] | |
| **Major bleeding** | **0 per 1000** | **0 per 1000** (0 to 0) | **RR 3.1** (0.13 to 73.14) | 343 (2 studies) | ⊕⊕⊖⊖ **low**[1,2,3] | |
| **Thrombocytopenia** | **202 per 1000** | **346 per 1000** (245 to 492) | **RR 1.71** (1.21 to 2.43) | 339 (2 studies) | ⊕⊕⊕⊖ **moderate**[1,2] | |
| **Quality of life** - not reported | See comment | See comment | Not estimable | - | See comment | |

*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% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Allocation concealed in 1 of the 3 trials. None of the studies blinded patients, providers or data collectors but 3 studies blinded outcome adjudicators. One study did not address incomplete data reporting. None of the studies was suspected of selective reporting. Two studies clearly used ITT.
[2] Small number of events
[3] CI includes values suggesting no effect and values suggesting either harm or benefit

**SoF References:**

1. Akl, E.A., et al., *Anticoagulation for patients with cancer and central venous catheters.* Cochrane Database Syst Rev, 2011(4): p. CD006468.
2. Lavau-Denes, S., et al., *Prophylaxis of catheter-related deep vein thrombosis in cancer patients with low-dose warfarin, low molecular weight heparin, or control: a randomized, controlled, phase III study.* Cancer Chemother Pharmacol, 2013. 72(1): p. 65-73.

Evidence to recommendation framework

***Guideline Question 6:*** *Should oral anticoagulation vs no anticoagulation be used in patients with cancer and central venous catheters?*

***Panelists in attendance:*** *Dr. Owaidah, Dr. Al Zahrani, Dr. Algahtani, Dr. Alsheef*

***Additional COI declared at the beginning of the meeting:*** *none declared*

***Population:*** cancer patients with central venous catheters
***Intervention:*** oral anticoagulation
***Comparison:*** No oral anticoagulation
***Setting:*** KSA
***Perspective:*** clinical or health system

***Background and Objective:*** Studies of oral anticoagulation in cancer patients with central venous catheters suggest a certain absolute risk increase of bleeding that outweighs a less certain absolute risk reduction of recurrent VTE. The effect on overall mortality is also less certain.

***Definition of population:*** Ambulatory cancer patients with CVC that are typically undergoing chemotherapy and/or radiotherapy, and have no typical indication for thromboprophylaxis (e.g., immobility)

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | KSA GUIDELINE PANEL CONSIDERATIONS |
|---|---|---|---|---|
| PROBLEM | Is the problem a priority? | No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐ | ***The baseline risks for the main outcomes of interest:*** | Do you think ***the baseline risk for any the outcomes of interest*** for the KSA guideline should be different? If yes, please provide your suggestions in the space provided in the table. Also provide citation, or at least a justification. ***Answer: no local data available*** **Priority of the problem: central line use is common. Patients already have cancer and dealing with chemo and thrombosis would be additional problem.** |

| Outcome | Assumed Baseline Risk in Systematic Review | Baseline risk suggested for KSA (if thought to be different) |
|---|---|---|
| Mortality (6 months) | 260 per 1000 | - |
| Symptomatic DVT (6 months) | 109 per 1000 | - |
| Major bleeding (6 months) | 2 per 1000 | - |
| Quality of life | Not available | - |

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | KSA GUIDELINE PANEL CONSIDERATIONS |
|---|---|---|---|---|
| BENEFITS & HARMS OF THE OPTIONS | **What is the overall quality of evidence?** | ☐ No included studies ☐ Very low ☒ Low ☐ Moderate ☐ High | ***The rating of the importance of the main outcomes of interest:*** | Do you think the ***rating of the importance of the main outcomes of interest*** for the KSA guideline should be different? If yes, please provide your suggestions in the space provided in the table. Also provide citation, or at least a justification. **Answer: No** |
| | **Is there important uncertainty about how much people value the main outcomes?** | ☐ Important uncertainty or variability ☐ Possibly important uncertainty or variability ☒ Probably no important uncertainty or variability ☐ No important uncertainty or variability ☐ No known undesirable outcomes | **Mortality** — **Relative importance**<br>Mortality — Critical<br>Symptomatic DVT — Critical<br>Major bleeding — Critical<br>Quality of life — Important | Do you think the ***values and preferences*** for the KSA guideline should be different? Please consider how would KSA patients accpet the intervention, how important they would find the differnet outcomes of interest, etc.<br>If yes, please provide your suggestions in the space provided in the table. Also provide citation, or at least a justification.<br>**Answer:**<br>**Oral anticoagulation requires frequent testing and monitoring, diet and medication restrictions, stoppage for procedures, etc. However, anticoagulation would be given for a relatively limited period of time**<br>**Patients would view potential reduction in mortality and symtomatic VTE favorably.** |
| | **Are the desirable anticipated effects large?** | ☐ No ☐ Probably No ☐ Uncertain ☒ Probably Yes ☐ Yes ☐ Varies | ***Summary of the evidence for patients' values and preferences:***<br>Not explicitly reported | |
| | **Are the undesirable anticipated effects small?** | ☐ No ☐ Probably No ☐ Uncertain ☒ Probably Yes ☐ Yes ☐ Varies | ***Summary of the relative effect of interventions (on both desirable and undesirable outcomes) and quality of evidence:***<br>Please see summary of findings and references | |
| | **Are the desirable effects large relative to undesirable effects?** | ☐ No ☐ Probably No ☐ Uncertain ☒ Probably Yes ☐ Yes ☐ Varies | | |

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | KSA GUIDELINE PANEL CONSIDERATIONS |
|---|---|---|---|---|
| | | | | Are you aware of ***any relevant studies*** that are not included in the summary of findings? **Answer: No**<br><br>**Note: Larger anticiapted effects for patients at high risk for VTE** |

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | KSA GUIDELINE PANEL CONSIDERATIONS |
|---|---|---|---|---|
| RESOURCE USE | **Are the resources required small?** | No ☐ / Probably No ☐ / Uncertain ☒ / Probably Yes ☐ / Yes ☐ / Varies ☐ | No evidence identified | What are the annual costs directly related to the intervention and complications in the KSA setting? Please provide your best (note whether in U.S Dollars or Saudi Arabian Riyal). **Answer: unit cost is low. Visits for monitoring, lab testing would reuire significant resources.**<br><br>Please suggest any relevant studies providing evidence about the use of resources (e.g., economic evaluations, cost-effectiveness, or resource utilization for the interventions in KSA). **Answer: None** |
| | **Is the incremental cost small relative to the net benefits?** | No ☐ / Probably No ☐ / Uncertain ☒ / Probably Yes ☐ / Yes ☐ / Varies ☐ | | |
| EQUITY | **What would be the impact on health inequities?** | Increased ☐ / Probably increased ☐ / Uncertain ☒ / Probably reduced ☐ / Reduced ☐ / Varies ☐ | No evidence identified | Based on your observations what would be the impact on ***health inequity*** if intervention were to be recommended (e.g. would health inequities be increased or reduced)? **Answer: None** |
| ACCEPTABILITY | **Is the option acceptable to key stakeholders?** | No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☒ / Yes ☐ / Varies ☐ | No evidence identified | Based on your observations what would be the ***acceptability*** of the intervention to be recommended (e.g. would the intervention be acceptable to stakeholders)? **Answer: Given it is relatively short period, more likely to be acceptable.** |

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | KSA GUIDELINE PANEL CONSIDERATIONS |
|---|---|---|---|---|
| FEASIBILITY | **Is the option feasible to implement?** | *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ ***Varies*** ☐ | No evidence identified | Based on your observations what would be the ***feasibility*** of the intervention to be recommended (e.g. would the intervention be acceptable to stakeholders)? **Answer: Patients would be coming back any way to take care of catheter** |

| | | | | | |
|---|---|---|---|---|---|
| **Balance of consequences** | Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐ | Undesirable consequences *probably outweigh* desirable consequences in most settings ☒ | The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐ | Desirable consequences *probably outweigh* undesirable consequences in most settings ☐ | Desirable consequences *clearly outweigh* undesirable consequences in most settings ☐ |

| Type of recommendation | We recommend against offering this option | We suggest not offering this option | We suggest offering this option | We recommend offering this option |
|---|---|---|---|---|
| | ☐ | ☒ | ☐ | ☐ |

**Recommendation (text)**

For outpatients with cancer and CVC, the KSA MoH guideline panel suggests against thromboprophylaxis with oral anticoagulation (weak recommendation; low quality evidence)
Key considerations:

- Use a validated tool (e.g., Khorana JNCCN 2011;9:789-798) to risk stratify patients, as those at 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)

| | |
|---|---|
| **Justification** | Low quality evidence suggests probable benefits |
| **Subgroup considerations** | None |
| **Implementation considerations** | - |
| **Monitoring and evaluation** | - |
| **Research priorities** | Research about new oral anticoagulants;<br>Studies comparing new oral anticoagulants vs. heparin<br>KSA cost-effectiveness studies |

**Summary of Findings (SoF) table:** oral anticoagulation vs no oral anticoagulation be used in cancer patients with central venous catheters

**VKA compared to no VKA for thrombosis prophylaxis 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
**Bibliography:** Akl et al. Anticoagulation for thrombosis prophylaxis in cancer patients with central venous catheters. Cochrane Database of Systematic Reviews. 2013 update identified one new trial [25,26]

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk **No VKA** | Corresponding risk **VKA** | | | | |
| **Death** | **260 per 1000** | **252 per 1000** (213 to 298) | **RR 0.97** (0.82 to 1.15) | 1371 (3 studies) | ⊕⊕⊖⊖ **low**[1,2] | |
| **Symptomatic DVT** | **109 per 1000** | **55 per 1000** (32 to 97) | **RR 0.51** (0.29 to 0.89) | 1513 (5 studies) | ⊕⊕⊕⊖ **moderate**[1,2] | |
| **Major bleeding** | **2 per 1000** | **13 per 1000** (2 to 103) | **RR 6.93** (0.86 to 56.08) | 1093 (2 studies) | ⊕⊕⊖⊖ **low**[1,2,3] | |
| **Quality of life** - not reported | See comment | See comment | Not estimable | - | See comment | |

*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% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Allocation concealed in 3 of the 5 trials. None of trials blinded patients, providers or data collectors and 3 trials blinded outcome adjudicators. 3 trials had no problem with missing data. Selective reporting was unclear in one trial. Three trials used intention to treat analysis.
[2] Small number of events
[3] CI includes values suggesting no effect and values suggesting either harm or benefit

## SoF References:

1. Akl, E.A., et al., *Anticoagulation for patients with cancer and central venous catheters.* Cochrane Database Syst Rev, 2011(4): p. CD006468.
2. Lavau-Denes, S., et al., *Prophylaxis of catheter-related deep vein thrombosis in cancer patients with low-dose warfarin, low molecular weight heparin, or control: a randomized, controlled, phase III study.* Cancer Chemother Pharmacol, 2013. 72(1): p. 65-73.

Evidence to recommendation framework

***Guideline Question 7:*** *Should Low Molecular Weight Heparin (LMWH) vs Unfractionated Heparin (UFH) be used in patients with cancer being initiated on treatment for venous thromboembolism?*

***Panelists in attendance:*** *Dr. Owaidah, Dr. Al Zahrani, Dr. Algahtani, Dr. Alsheef*

***Additional COI declared at the beginning of the meeting:*** *none declared*

***Problem:*** patients with cancer being initiated on treatment for venous thromboembolism
***Intervention:*** LMWH
***Comparison:*** UFH
***Setting:*** KSA
***Perspective:*** clinical or health system

***Background and Objective:*** The evidence suggests that LMWH is associated with decreased mortality, lower recurrence of VTE and decreased incidence of major bleeding compared with IV UFH

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | KSA GUIDELINE PANEL CONSIDERATIONS |
|---|---|---|---|---|
| PROBLEM | **Is the problem a priority?** | *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ *Varies* ☐ | ***The baseline risks for the main outcomes of interest:*** | Do you think ***the baseline risk for any the outcomes of interest*** for the KSA guideline should be different? If yes, please provide your suggestions in the space provided in the table. Also provide citation, or at least a justification. ***Answer: no local data available*** |

| Outcome | Assumed Baseline Risk in Systematic Review | Baseline risk suggested for KSA (if thought to be different) |
|---|---|---|
| Mortality (3 months) | 189 per 1000 | - |
| Recurrent VTE (3 months) | 96 per 1000 | - |
| Major bleeding (3 months) | 15 per 1000 | - |

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | KSA GUIDELINE PANEL CONSIDERATIONS |
|---|---|---|---|---|
| BENEFITS & HARMS OF THE OPTIONS | **What is the overall quality of evidence?** | No included studies ☐ \| Very low ☒ \| Low ☐ \| Moderate ☐ \| High ☐ | ***The rating of the importance of the main outcomes of interest:*** | Do you think the ***rating of the importance of the main outcomes of interest*** for the KSA guideline should be different? If yes, please provide your suggestions in the space provided in the table. Also provide citation, or at least a justification. **Answer: No** |
| | **Is there important uncertainty about how much people value the main outcomes?** | Important uncertainty or variability ☐ \| Possibly important uncertainty or variability ☐ \| Probably no important uncertainty or variability ☐ \| No important uncertainty or variability ☒ \| No known undesirable outcomes ☐ | **Outcome** — **Relative importance**<br>Mortality — Important<br>Recurrent VTE — Critical<br>Major bleeding — Critical<br><br>***Summary of the evidence for patients' values and preferences:***<br><br>Not explicitly reported | Do you think the ***values and preferences*** for the KSA guideline should be different? Please consider how would KSA patients accpet the intervention, how important they would find the differnet outcomes of interest, etc.<br>If yes, please provide your suggestions in the space provided in the table. Also provide citation, or at least a justification. **Answer: Patients preferences with relation to intravenous versus subcutaneous injections might vary, but the majority would value being discharged early.** |
| | **Are the desirable anticipated effects large?** | No ☐ \| Probably No ☐ \| Uncertain ☐ \| Probably Yes ☒ \| Yes ☐ \| ***Varies*** ☐ | | |
| | **Are the undesirable anticipated effects small?** | No ☐ \| Probably No ☐ \| Uncertain ☐ \| Probably Yes ☒ \| Yes ☐ \| ***Varies*** ☐ | ***Summary of the relative effect of interventions (on both desirable and undesirable outcomes) and quality of evidence*:**<br>Please see summary of findings and references | Are you aware of ***any relevant studies*** that are not included in the evidence summary of findings? **Answer: No** |
| | **Are the desirable effects large relative to undesirable effects?** | No ☐ \| Probably No ☐ \| Uncertain ☐ \| Probably Yes ☒ \| Yes ☐ \| ***Varies*** ☐ | | |

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | KSA GUIDELINE PANEL CONSIDERATIONS |
|---|---|---|---|---|
| RESOURCE USE | **Are the resources required small?** | No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☒ / Yes ☐ / Varies ☐ | No direct evidence identified<br>Probably yes due to indirect evidence | **Indirect evidence from 2 studies of DVT treatment at home:**<br>**Algahtani 2013:[8]**<br>• **Prospective study of 61 DVT cases presenting to ED (Aug 2009-Aug 2010) (KKUH)**<br>• **Mean outpatient cost was significantly lower ($1750 vs. $4338).**<br>**Aleissi 2013:[16]**<br>• **Retrospective chart analysis of DVT cases between 2005 and 2012 (KAMC)**<br>• **Of 190 DVT patients, 80 (42%) were eligible for outpatient management.**<br>**Average length of stay was 7.88 days. 78.75 bed days would have been saved per year. Cost savings would be SR 118,125 per year** |
| RESOURCE USE | **Is the incremental cost small relative to the net benefits?** | No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☒ / Yes ☐ / Varies ☐ | | |
| EQUITY | **What would be the impact on health inequities?** | Increased ☐ / Probably increased ☐ / Uncertain ☐ / Probably reduced ☒ / Reduced ☐ / Varies ☐ | No evidence identified | Based on your observations what would be the impact on ***health inequity*** if intervention were to be recommended (e.g. would health inequities be increased or reduced)? **Answer: probably reduced due to health expenditures savings and having more beds available** |
| ACCEPTABILITY | **Is the option acceptable to key stakeholders?** | No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐ | No evidence identified | Based on your observations what would be the ***acceptability*** of the intervention to be recommended (e.g. would the intervention be acceptable to stakeholders)? **Answer: Yes** |

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | KSA GUIDELINE PANEL CONSIDERATIONS |
|---|---|---|---|---|
| FEASIBILITY | **Is the option feasible to implement?** | *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ \| ***Varies*** ☐ | No evidence identified | Based on your observations what would be the ***feasibility*** of the intervention to be recommended (e.g. would the intervention be acceptable to stakeholders)? **Answer: Yes** |

| | | | | | |
|---|---|---|---|---|---|
| **Balance of consequences** | Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐ | Undesirable consequences *probably outweigh* desirable consequences in most settings ☐ | The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐ | Desirable consequences *probably outweigh* undesirable consequences in most settings ☒ | Desirable consequences *clearly outweigh* undesirable consequences in most settings ☐ |

| | | | | |
|---|---|---|---|---|
| **Type of recommendation** | We recommend against offering this option | We suggest not offering this option | We suggest offering this option | We recommend offering this option |
| | ☐ | ☐ | ☒ | ☐ |

| | |
|---|---|
| **Recommendation (text)** | In patients with cancer being initiated on treatment for venous thromboembolism, the KSA MOH panel suggests LMWH over IV UFH (conditional recommendation; very low quality evidence) |
| **Justification** | This recommendation is conditional mainly due to the very low quality evidence |
| **Subgroup considerations** | None |
| **Implementation considerations** | - |
| **Monitoring and evaluation** | - |
| **Research priorities** | Studies comparing LMWH to IV UFH<br>Studies comparing initiation of VTE treatment with heparin versus NOACs |

**Summary of Findings (SoF) table:** LMWH compared to UFH for the initial treatment of venous thromboembolism in patients with cancer

**LMWH compared to UFH 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
**Bibliography:** Akl et al. Anticoagulation for the initial treatment of venous thromboembolism in patients with cancer. Cochrane Database of Systematic Reviews. 2013 update [27]

| Outcomes | Illustrative comparative risks* (95% CI) Assumed risk UFH | Corresponding risk LMWH | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| **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**[1,2,3] | |
| **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**[3,4,5] | |
| **Major bleeding** - not reported | See comment | See comment | Not estimable | - | See comment | There is indirect evidence that both LMWH and UFH increase the risk of major bleeding compared with no anticoagulation |
| **Post phlebitic syndrome** - not reported | See comment | See comment | Not estimable | - | See comment | |
| **Quality of life** - not reported | See comment | See comment | Not estimable | - | See comment | |
| **Thrombocytopenia** - not reported | See comment | See comment | Not estimable | - | See comment | |

*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% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Of the 11 studies, 10 clearly concealed allocation, one blinded patients, providers or data collectors, 11 blinded outcome adjudicators, and 10 used ITT.
[2] A relatively small number of events
[3] We excluded 11 studies from the systematic review because the data for the cancer subgroup analysis was not reported. Of the 13 included studies, only three reported on the recurrence VTE outcome. An analysis of the same question not restricted to patients with cancer, demonstrated a likely publication bias in favor of LMWH.
[4] Of the 3 studies, 2 clearly concealed allocation, none blinded patients, providers or data collectors, 3 blinded outcome adjudicators, and 2 used ITT.
[5] CI includes values suggesting benefit and values suggesting harm

**SoF References:**

1. Algahtani, F., et al., *Hospital versus home treatment of deep vein thrombosis in a tertiary care hospital in Saudi Arabia: Are we ready?* Saudi Pharm J, 2013. 21(2): p. 165-8.
2. Salih, A. and G. Hosny, *Impact of an out-patient based strategy for the management of acute deep venous thrombosis in Saudi Arabia.* European Journal of Internal Medicine, 2013. 24: p. e170.
3. Akl, E.A., et al., *Anticoagulation for the initial treatment of venous thromboembolism in patients with cancer.* Cochrane Database Syst Rev, 2011(6): p. CD006649.

Evidence to recommendation framework

***Guideline Question 8:*** *Should heparin vs oral anticoagulation be used in patients with cancer requiring long term treatment of venous thromboembolism?*

***Panelists in attendance:*** Dr. Alghatani, Dr. Alsheef, Dr. AlMomen

***Additional COI declared at the beginning of the meeting:*** Dr. Alghatani and Dr. Alzahrani involved in CATCH study centre

***Problem:*** patients with cancer requiring long term treatment of venous thromboembolism
***Option:*** Heparin treatment
***Comparison:*** No heparin treatment
***Setting:*** KSA
***Perspective:*** clinical or health system

***Background and Objective:*** Based on published evidence, it is possible that the response to LMWH versus VKA therapy may differ between patients with cancer and without cancer (recurrent VTE: RR 0.52 with cancer [95%CI 0.36 to 0.76] versus 0.99 without cancer [95%CI 0.46 to 2.13]); major bleeding: RR 0.92 with cancer [95%CI 0.59 to 1.44] vs. 0.43 without cancer [95%CI 0.16 to 1.17]); mortality: RR 0.93 with cancer [95%CI 0.79 to 1.09] vs. 1.85 without cancer [95%CI 0.59 to 5.77]).

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | KSA GUIDELINE PANEL CONSIDERATIONS |
|---|---|---|---|---|
| PROBLEM | **Is the problem a priority?** | *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ *Varies* ☐ | ***The baseline risks for the main outcomes of interest:*** | Do you think ***the baseline risk for any the outcomes of interest*** for the KSA guideline should be different? If yes, please provide your suggestions in the space provided in the table. Also provide citation, or at least a justification. ***Answer: no local data available*** |

| Outcome | Assumed Baseline Risk in Systematic Review | Baseline risk suggested for KSA (if thought to be different) |
|---|---|---|
| Mortality (6 months) | 164 per 1000 | - |
| Recurrent VTE (6 months) | 80 to 200 per 1000 | - |
| Major bleeding (6 months) | 20 to 80 per 1000 | - |
| PTS (2 years) | 705 | - |

BENEFITS & HARMS OF THE OPTIONS

| CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | KSA GUIDELINE PANEL CONSIDERATIONS |
|---|---|---|---|
| **What is the overall quality of evidence?** | No included studies ☐ \| Very low ☐ \| Low ☐ \| Moderate ☒ \| High ☐ | ***The rating of the importance of the main outcomes of interest:*** | Do you think the ***rating of the importance of the main outcomes of interest*** for the KSA guideline should be different? If yes, please provide your suggestions in the space provided in the table. Also provide citation, or at least a justification. **Answer: No** |
| **Is there important uncertainty about how much people value the main outcomes?** | Important uncertainty or variability ☐ \| Possibly important uncertainty or variability ☐ \| Probably no important uncertainty or variability ☒ \| No important uncertainty or variability ☐ \| No known undesirable outcomes ☐ | | |
| **Are the desirable anticipated effects large?** | No ☐ \| Probably No ☐ \| Uncertain ☐ \| Probably Yes ☒ \| Yes ☒ \| Varies ☐<br>*Non-metastatic: Probably Yes*<br>*Metastatic: Yes* | | Do you think the ***values and preferences*** for the KSA guideline should be different? Please consider how would KSA patients accpet the intervention, how important they would find the differnet outcomes of interest, etc.<br>If yes, please provide your suggestions in the space provided in the table. Also provide citation, or at least a justification.<br>**Answer: Patients may assign different values to the burden of warfarin versus LMWH. They typically assign a high value to avoiding PTS.** |
| **Are the undesirable anticipated effects small?** | No ☐ \| Probably No ☐ \| Uncertain ☐ \| Probably Yes ☒ \| Yes ☒ \| Varies ☐<br>*Non-metastatic: Yes*<br>*Metastatic: Probably Yes* | | |
| **Are the desirable effects large relative to undesirable effects?** | No ☐ \| Probably No ☐ \| Uncertain ☐ \| Probably Yes ☒ \| Yes ☒ \| Varies ☐<br>*Non-metastatic: Probably Yes*<br>*Metastatic: Yes* | | Are you aware of ***any relevant studies*** that are not included in the evidence summary of findings? **Answer: no** |

| Outcome | Relative importance |
|---|---|
| Mortality | Important |
| Recurrent VTE | Critical |
| Major bleeding | Critical |
| Burden of anticoagulation | Important |
| PTS | Important |

***Summary of the evidence for patients' values and preferences:***

Burden considered:

- Warfarin: Daily medication, dietary interactions, frequent blood testing/monitoring, increased hospital/clinic visits
- LMWH: Daily injection. No dietary interactions, no frequent blood testing/monitoring

The panel considered that most patients prefer VKA therapy over LMWH therapy. The panel also considered from the evidence that the choice of treatment in patients with and without cancer is sensitive to individual patient's tolerance for daily injections, need for laboratory monitoring, and treatment costs.

***Summary of the relative effect of interventions (on both desirable and undesirable outcomes) and quality of evidence*:**
Please see summary of findings and references

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | KSA GUIDELINE PANEL CONSIDERATIONS |
|---|---|---|---|---|
| RESOURCE USE | **Are the resources required small?** | No ☐ / Probably No ☐ / Uncertain ☒ / Probably Yes ☐ / Yes ☐ / Varies ☐ | ***Summary of the resource use evidence***<br>No evidence identified<br>The panel considered from the evidence that the higher purchase cost of LMWH compared to VKA therapy is an additional barrier to the long-term use of LMWH. | What are the annual costs directly related to the intervention and complications in the KSA setting? Please provide your best (note whether in U.S Dollars or Saudi Arabian Riyal). **Answer: LMWH more expensive than warfarin. Oral require monitoring, testing, frequent visits to the clinic.**<br><br>Please suggest any relevant studies providing evidence about the use of resources (e.g., economic evaluations, cost-effectiveness, or resource utilization for the interventions in KSA). **Answer: None** |
| | **Is the incremental cost small relative to the net benefits?** | No ☐ / Probably No ☐ / Uncertain ☒ / Probably Yes ☐ / Yes ☐ / Varies ☐ | | |
| EQUITY | **What would be the impact on health inequities?** | Increased ☐ / Probably increased ☐ / Uncertain ☒ / Probably reduced ☐ / Reduced ☐ / Varies ☐ | No evidence identified | Based on your observations what would be the impact on ***health inequity*** if intervention were to be recommended (e.g. would health inequities be increased or reduced)? **Answer: Patients on heparin less likely to be readmitted, less frequent visit (i.e. freeing up beds).** |
| ACCEPTABILITY | **Is the option acceptable to key stakeholders?** | No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☒ / Yes ☐ / Varies ☐ | No evidence identified | Based on your observations what would be the ***acceptability*** of the intervention to be recommended (e.g. would the intervention be acceptable to stakeholders)? **Answer: Probably yes** |

| | CRITERIA | JUDGEMENTS | RESEARCH EVIDENCE | KSA GUIDELINE PANEL CONSIDERATIONS |
|---|---|---|---|---|
| FEASIBILITY | **Is the option feasible to implement?** | *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐ | No evidence identified | Based on your observations what would be the ***feasibility*** of the intervention to be recommended (e.g. would the intervention be acceptable to stakeholders)? **Answer: This is current practice to use LMWH, therefore feasible and acceptable based on experience of the panel.** |

| | | | | | |
|---|---|---|---|---|---|
| **Balance of consequences** | Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐ | Undesirable consequences *probably outweigh* desirable consequences in most settings ☐ | The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐ | Desirable consequences *probably outweigh* undesirable consequences in most settings **(Non-metastatic)** ☒ | Desirable consequences *clearly outweigh* undesirable consequences in most settings **(Metastatic)** ☒ |

| | | | | |
|---|---|---|---|---|
| **Type of recommendation** | We recommend against offering this option ☐ | We suggest not offering this option ☐ | We suggest offering this option **(Non-metastatic)** ☒ | We recommend offering this option **(Metastatic)** ☒ |

**Recommendation (text)**

In patients with metastatic cancer requiring long term treatment of venous thromboembolism, the KSA MoH panel recommends LMWH over VKA (strong recommendation; moderate quality evidence)

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

Key considerations:

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

| | |
|---|---|
| **Justification** | Moderate quality evidence shows that the desirable consequences clearly outweigh undesirable consequences amongst patients with metastatic cancer, but to a lesser degree amongst patients with non-metastatic cancer. |
| **Subgroup considerations** | By cancer status (metastatic versus non-metastatic) as detailed above |
| **Implementation considerations** | Consistent with current practice, nothing required at administrative level. |
| **Monitoring and evaluation** | Close monitoring for VKA therapy<br>Monitoring of renal function and platelet count for LMWH therapy. |
| **Research priorities** | New oral anticoagulants vs. LMWH |

**Summary of Findings (SoF) table:** heparin vs no oral anticoagulation in patients with cancer requiring long term treatment of venous thromboembolism

**LMWH compared to VKA for long term treatment of patients with VTE**

**Patient or population:** patients with long term treatment of patients with VTE
**Settings:** outpatient
**Intervention:** LMWH[1,2]
**Comparison:** VKA
**Bibliography:** Included studies: Deitcher et al[31], Hull et al [32], Hull et al[33], Lee et al[34], Lopaciuk et al[35], Lopez-Beret et al [36], Meyer G et al[37], Romera et al[38] Two of these studies enrolled only patients without cancer[33,36], 3 enrolled only patients with cancer[37,31,34], and 3 enrolled both patients with and without cancer[32,35,38] (separate data provided for cancer and non-cancer patients in one study[32,39]). Excluded studies (less than 50% of therapeutic dose LMWH during extended phase): Pini et al[40], Das et al[41], Gonzalez-Fajardo et al[42], Veiga et al[43], Kakkar et al[44], (Cesarone 2003 Circ abstract). PTS data from: Hull et al[33]

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk **VKA** | Corresponding risk **LMWH** | | | | |
| **Death**<br>Follow-up: median 6 months | **164 per 1000** | **158 per 1000**<br>(133 to 185) | **RR 0.96**<br>(0.81 to 1.13) | 2496<br>(7 studies) | ⊕⊕⊕⊖<br>**moderate**[3,4] | |
| **Recurrent VTE**<br>Follow-up: median 6 months | **Low**[5] | | **RR 0.62**<br>(0.46 to 0.84) | 2727<br>(8 studies) | ⊕⊕⊕⊖<br>**moderate**[6] | |
| | **30 per 1000** | **19 per 1000**<br>(14 to 25) | | | | |
| | **Moderate**[5] | | | | | |
| | **80 per 1000** | **50 per 1000**<br>(37 to 67) | | | | |
| | **High**[5] | | | | | |
| | **200 per 1000** | **124 per 1000**<br>(92 to 168) | | | | |
| **Major bleeding**<br>Follow-up: median 6 months | **Low**[7] | | **RR 0.81**<br>(0.55 to 1.2) | 2737<br>(8 studies) | ⊕⊕⊕⊖<br>**moderate**[8,9] | |
| | **20 per 1000** | **16 per 1000**<br>(11 to 24) | | | | |
| | **High**[7] | | | | | |
| | **80 per 1000** | **65 per 1000**<br>(44 to 96) | | | | |
| **PTS**<br>Self-reported leg symptoms and signs<br>Follow-up: median 2 years | **Moderate**[10] | | **RR 0.85**<br>(0.77 to 0.94) | 100<br>(1 study) | ⊕⊕⊖⊖<br>**low**[11,12] | |
| | **200 per 1000** | **170 per 1000**<br>(154 to 188) | | | | |

*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% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Limited to LMWH treatments that consisted of 50% or more of the dose of the acute treatment phase, used for the extended treatment phase
[2] Initial parenteral anticoagulation was similar in both arms for all trials except one (Hull 2007). In Hull 2007 participants in the LMWH arm received initially the same LWMH whereas patients randomized to oral anticoagulation initially received UFH
[3] 1 study did not report deaths, which could reflect selective reporting of outcomes.
[4] Confidence interval includes values suggestion no effect and values suggesting harm with LMWH
[5] Low risk of recurrent VTE corresponds to patients without cancer (3% estimate taken from recent large RCTs of acute treatment), intermediate risk of recurrent VTE corresponds to patients with local or recently resected cancer (based on average rate across 6 trials included in analysis; consistent with Prandoni [particularly if low risk is increased to 4%]), and high risk of recurrent VTE corresponds to patients with locally advanced or distant metastatic cancer. (Prandoni et al 2002)
[6] None of the studies was blinded and the diagnosis of VTE has a subjective component. Also, there could be a lower threshold for diagnosis of VTE in patients treated with oral anticoagulants as switching the treatment of these patients to LMWH is common practice. Also, there is reluctance to diagnose recurrent VTE in patients already on LMWH (given the absence of an acceptable alternative therapeutic option).
[7] Based on Prandoni et al, RIETE, Byeth et al: Low risk of bleeding corresponds absence of any risk factor for bleeding (i.e., > 75 years, cancer, metastatic disease; chronic renal or hepatic failure; platelet count <80,0000; requires antiplatelet therapy; history of bleeding without a reversible cause).
[8] None of studies was blinded, major bleeding diagnosis has a subjective component
[9] 95% confidence intervals for the risk ratio for major bleeding includes values suggesting clinically important decrease or increase with LMWH
[10] Baseline risk assumes that patients all wear pressure stockings
[11] Participants and investigators not blinded. Leg symptoms after 3 months of treatment were self-reported
[12] There uncertainty about the association between leg symptoms and signs at 3 months and long-term PTS

A newly identified study (van Doormaal 2010; dissertation) compared Idraparinux to standard therapy in the treatment of DVT in cancer patients;[29] including the study in the meta-analysis did not substantially affect the results for mortality (RR 0.95 [0.82, 1.11]) or VTE (RR 0.48 [0.34, 0.67]) or major bleeding (RR 1.05 [0.63, 1.77])

## SoF References:

1. Deitcher, S.R., et al., *Secondary prevention of venous thromboembolic events in patients with active cancer: enoxaparin alone versus initial enoxaparin followed by warfarin for a 180-day period.* Clin Appl Thromb Hemost, 2006. 12(4): p. 389-96.
2. Hull, R.D., et al., *Self-managed long-term low-molecular-weight heparin therapy: the balance of benefits and harms.* Am.J.Med., 2007. 120(1): p. 72-82.
3. Hull, R.D., et al., *Home therapy of venous thrombosis with long-term LMWH versus usual care: patient satisfaction and post-thrombotic syndrome.* Am J Med, 2009. 122(8): p. 762-769 e3.

4. Lee, A.Y., et al., *Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer.* N.Engl.J Med, 2003. 349(2): p. 146-153.
5. Lopaciuk, S., et al., *Low molecular weight heparin versus acenocoumarol in the secondary prophylaxis of deep vein thrombosis.* Thrombosis and Haemostasis, 1999. 81: p. 26-31.
6. Lopez-Beret, P., et al., *Low molecular weight heparin versus oral anticoagulants in the long- term treatment of deep venous thrombosis.* J Vasc.Surg., 2001. 33(1): p. 77-90.
7. Meyer, G., et al., *Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study.* Archives of Internal Medicine, 2002. 162(15): p. 1729-1735.
8. Romera, A., et al., *A randomised open-label trial comparing long-term sub-cutaneous low-molecular-weight heparin compared with oral-anticoagulant therapy in the treatment of deep venous thrombosis.* Eur J Vasc Endovasc Surg, 2009. 37(3): p. 349-56.
9. Hull, R.D., et al., *Long-term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer.* Am.J.Med., 2006. 119(12): p. 1062-1072.
10. Pini, M., et al., *Low molecular weight heparin versus warfarin the prevention of recurrence after deep vein thrombosis.* Thrombosis and Haemostasis, 1994. 72(2): p. 191-197.
11. Das, S.K., et al., *Low-molecular-weight heparin versus warfarin for prevention of recurrent venous thromboembolism: A randomized trial.* World J.Surg., 1996. 20: p. 521-527.
12. Gonzalez-Fajardo, J.A., et al., *Venographic comparison of subcutaneous low-molecular weight heparin with oral anticoagulant therapy in the long-term treatment of deep venous thrombosis.* J Vasc.Surg., 1999. 30(2): p. 283-292.
13. Veiga, F., et al., *Low molecular weight heparin (enoxaparin) versus oral anticoagulant therapy (acenocoumarol) in the long-term treatment of deep venous thrombosis in the elderly: a randomized trial.* Thromb.Haemost., 2000. 84(4): p. 559-564.
14. Kakkar, V., et al., *Low-molecular-weight heparin in the acute and long-term treatment of deep vein thrombosis.* Thrombosis and Haemostasis, 2003. 89(4): p. 674-680.
15. van Doormaal, F.F., et al., *Idraparinux versus standard therapy in the treatment of deep venous thrombosis in cancer patients: a subgroup analysis of the Van Gogh DVT trial.* Thromb Haemost, 2010. 104(1): p. 86-91.

## Appendix 2: Search Strategies and Results

### 1. Should home treatment vs. hospital treatment be used for patients with acute DVT of the leg?

| Database: **Cochrane Library CENTRAL** | |
|---|---|
| **Search strategy:** | **Date of search: 11/2013** |
| #1 MeSH descriptor Thromboembolism explode all trees<br>#2 deep near ve* near thrombo*<br>#3 ve* near thrombo*<br>#4 (#1 OR #2 OR #3)<br>#5 MeSH descriptor Heparin explode all trees<br>#6 low near molecul* near weight near heparin*<br>#7 heparin*<br>#8 unfractionat* near heparin*<br>#9 (#5 OR #6 OR #7 OR #8)<br>#10 home<br>#11 home near therap*<br>#12 inpatient* near therap*<br>#13 inpatient* and therap*<br>#14 (#10 OR #11 OR #12 OR #13)<br>#15 (#4 AND #9 AND #14)<br><br>Date limit: 01/2012 - 11/2013<br><br>Study Types: RCTs | |
| **Records Retrieved: 53** | |

| Database: **MEDLINE** | |
|---|---|
| **Search strategy:** | **Date of search: 11/2013** |
| 1 exp Thromboembolism/<br>2 (deep adj ve* adj thrombo*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]<br>3 (ve* adj thrombo*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]<br>4 1 or 2 or 3<br>5 exp Heparin/<br>6 (low adj molecul* adj weight adj heparin*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]<br>7 heparin*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]<br>8 (unfractionat* adj heparin*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]<br>9 5 or 6 or 7 or 8<br>10 home.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]<br>11 (home adj therap*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] | |

12 (inpatient* adj therap*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
13 (inpatient* and therap*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
14 10 or 11 or 12 or 13
15 4 and 9 and 14
16 randomized controlled trial.pt.
17 controlled clinical trial.pt.
18 randomized.ab.
19 placebo.ab.
20 clinical trials as topic.sh.
21 randomly.ab.
22 trial.ti.
23 16 or 17 or 18 or 19 or 20 or 21 or 22
24 exp animals/ not humans.sh.
25 23 not 24
26 15 and 25
Date limit: 01/2012 - 11/2013

Study Types: RCTs

| **Records Retrieved: 90** | |
|---|---|

| Database: **EMBASE** | |
|---|---|
| **Search strategy:** | **Date of search: 11/2013** |

1. exp Thromboembolism/
2. (deep adj ve* adj thrombo*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
3. (ve* adj thrombo*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
4. 1 or 2 or 3
5. exp Heparin/
6. (low adj molecul* adj weight adj heparin*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
7. heparin*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
8. (unfractionat* adj heparin*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
9. 5 or 6 or 7 or 8
10. home.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
11. (home adj therap*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
12. (inpatient* adj therap*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
13. (inpatient* and therap*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
14. 10 or 11 or 12 or 13
15. 4 and 9 and 14
16. limit 15 to yr="2012 - 2013"
17. (((((random$ or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or doubl$) adj blind$) or singl$) adj blind$) or assign$ or allocat$ or volunteer$).mp. [mp=title, abstract, subject headings, heading word,

| |
|---|
| drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]<br>18. crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]<br>19. 17 or 18<br>20. 16 and 19<br>Date limit: 01/2012 - 11/2013<br><br>Study Types: RCTs |
| **Records Retrieved: 5** |

| Database: **CINAHL** | |
|---|---|
| **Search strategy:** | **Date of search: 11/2013** |
| S7 S1 AND S2 AND S5<br>S6 S1 AND S2 AND S5<br>S5 S3 OR S4<br>S4 (MM "Inpatients")<br>S3 (MM "Home Health Care+")<br>S2 (MH "Heparin+") OR (MM "Heparin, Low-Molecular-Weight+")<br>S1 (MM "Thromboembolism+") OR (MM "Venous Thromboembolism")<br>Date limit: 01/2012 - 11/2013<br><br>Study Types: RCTs | |
| **Records Retrieved: 0** | |

| | |
|---|---|
| **Total No. Retrieved:** | **148** |
| Cochrane: | 53 |
| Medline: | 90 |
| Embase: | 5 |
| Others: CINAHL | 0 |
| **Duplicates:** | 1 |
| **No. Total** Without duplicates**:** | **147** |

2. **Should early discharge vs. standard discharge be used for patients with acute PE?**

| Database: **Cochrane Library CENTRAL** | |
|---|---|
| **Search strategy:** | **Date of search: 11/2013** |
| #1 Pulmonary embolism<br>#2 Thromboembolism<br>#3 Ambulatory care<br>#4 Outpatients<br>#5 #1 OR #2<br>#6 #3 Or #4<br>#7 #5 AND #6<br><br>Date limit: 01/2012 - 11/2013<br><br>Study Types: RCTs | |
| **Records Retrieved: 5** | |

| Database: **MEDLINE** | |
|---|---|
| **Search strategy:** | **Date of search: 11-2013** |
| 1 "pulmonary embolism".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]<br>2 Pulmonary Embolism/<br>3 thromboembolism.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]<br>4 Venous Thromboembolism/ or Thromboembolism/<br>5 1 or 2 or 3 or 4<br>6 "ambulatory care".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]<br>7 Ambulatory Care/<br>8 "outpatient".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]<br>9 "outpatients".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]<br>10 Outpatients/<br>11 6 or 7 or 8 or 9 or 10<br>12 5 and 11<br>13 5 and 11<br>14 limit 13 to yr="2012 -Current"<br>15 randomized controlled trial.pt.<br>16 controlled clinical trial.pt.<br>17 randomized.ab.<br>18 placebo.ab.<br>19 clinical trials as topic.sh.<br>20 randomly.ab.<br>21 trial.ti.<br>22 15 or 16 or 17 or 18 or 19 or 20 or 21<br>23 exp animals/ not humans.sh.<br>24 22 not 23<br>25 14 and 24<br>Date limit: 01/2012 - 11/2013 | |

| |
|---|
| Study Types: RCTs |
| **Records Retrieved: 23** |

| Database: **EMBASE** | |
|---|---|
| **Search strategy:** | **Date of search: 11/2013** |

1 "pulmonary embolism".mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
2 lung embolism/
3 "thromboembolism".mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
4 thromboembolism/ or venous thromboembolism/
5 1 or 2 or 3 or 4
6 "ambulatory care".mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
7 ambulatory care/
8 "outpatient".mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
9 "outpatients".mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
10 outpatient/
11 6 or 7 or 8 or 9 or 10
12 5 and 11
13 limit 12 to yr="2012 - 2013"
14 (((((random$ or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or doubl$) adj blind$) or singl$) adj blind$) or assign$ or allocat$ or volunteer$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
15 crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
16 14 or 15
17 13 and 16
Date limit: 01/2012 - 11/2013

Study Types: RCTs

| |
|---|
| **Records Retrieved:22** |

| Database: **CINAHL** | |
|---|---|
| **Search strategy:** | **Date of search: 11/2013** |

S8 S5 AND S6
S7 S5 AND S6
S6 S3 OR S4
S5 S1 OR S2
S4 (MM "Outpatients")
S3 (MM "Ambulatory Care")
S2 (MM "Pulmonary Embolism")
S1 (MM "Thromboembolism")
Date limit: 01/2009 - 11/2003

Study Types: RCTs

| | |
|---|---|
| **Records Retrieved: 1** | |

| | |
|---|---|
| **Total No. Retrieved:** | **51** |
| Cochrane: | 5 |
| Medline: | 23 |
| Embase: | 22 |
| Others: CINAHL | 1 |
| **Duplicates:** | 7 |
| **No. Total** Without duplicates**:** | **44** |

3. **Should heparin vs no heparin be used in outpatients with cancer who have no other therapeutic or prophylactic indication for anticoagulation?**

| Database: **Cochrane Library** | |
|---|---|
| **Search strategy:** | **Date of search: 12/2013** |
| #1 MeSH descriptor: [Heparin] explode all trees<br>#2 (LMWH or heparin or nadroparin or fraxiparin or enoxaparin or clexane or lovenox or dalteparin or fragmin or ardeparin or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin or danaproid or orgaran or bemiparin or hibor, badyket, semuloparin, parnaparin, fluxum)<br>#3 MeSH descriptor: [Coumarins] explode all trees<br>#4 (warfarin or coumadin or acenocumarol or phenprocumon or 4-hydroxicoumarins or oral anticoagulant or vitamin K antagonist or VKA)<br>#5 (fondaparinux or arixtra)<br>#6 (ximelagatran or exanta)<br>#7 (pradaxa or dabigatran or rivaroxaban or xarelto or apixaban or eliquis or edoxaban or lixiana or betrixaban or edoxaban or otamixaban)<br>#8 #1 or #2 or #3 or #4 or #5 or #6 or #7<br>#9 MeSH descriptor: [Neoplasms] explode all trees<br>#10 (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*)<br>#11 #9 or #10<br>#12 #8 and #10<br><br>Date limit: 01/2010 - 12/2013<br>Study Types: RCT | |
| **Records Retrieved: 511** | |

| Database: **MEDLINE** | |
|---|---|
| **Search strategy:** | **Date of search: 12/2013** |
| #1 exp Heparin/<br>#2 (LMWH or heparin or nadroparin or fraxiparin or enoxaparin or clexane or lovenox or dalteparin or fragmin or ardeparin or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin or danaproid or orgaran or bemiparin or hibor, badyket, semuloparin, parnaparin, fluxum).tw.<br>#3 exp Coumarins/<br>#4 (warfarin or coumadin or acenocumarol or phenprocumon or 4-hydroxicoumarins or oral anticoagulant or vitamin K antagonist or VKA).tw.<br>#5 (fondaparinux or arixtra).tw.<br>#6 (ximelagatran or exanta).tw.<br>#7 (pradaxa or dabigatran or rivaroxaban or xarelto or apixaban or eliquis or edoxaban or lixiana or betrixaban or edoxaban or otamixaban).tw.<br>#8 1 or 2 or 3 or 4 or 5 or 6 or 7<br>#9 exp Neoplasms/<br>#10 (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*).tw.<br>#11 9 or 10<br>#12 8 and 11<br>#13 randomized controlled trial.pt.<br>#14 controlled clinical trial.pt.<br>#15 randomized.ab.<br>#16 placebo.ab.<br>#17 drug therapy.fs.<br>#18 randomly.ab.<br>#19 trial.ab. | |

| |
|---|
| #20 groups.ab.<br>#21 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20<br>#22 12 and 21<br>#23 exp animals/ not humans.sh.<br>#24 22 not 23<br><br>Date limit: 01/2010 - 12/2013<br>Study Types: RCT |
| **Records Retrieved: 602** |

| Database: **EMBASE** | |
|---|---|
| **Search strategy:** | **Date of search: 12/2013** |
| #1 heparin/<br>#2 exp low molecular weight heparin/<br>#3 (LMWH or heparin or nadroparin or fraxiparin or enoxaparin or clexane or lovenox or dalteparin or fragmin or ardeparin or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin or danaproid or orgaran or bemiparin or hibor, badyket, semuloparin, parnaparin, fluxum).tw.<br>#4 exp coumarin derivative/<br>#5 (warfarin or coumadin or acenocumarol or phenprocumon or 4-hydroxicoumarins or oral anticoagulant or vitamin K antagonist or VKA).tw.<br>#6 (fondaparinux or arixtra).tw.<br>#7 (ximelagatran or exanta).tw.<br>#8 (pradaxa or dabigatran or rivaroxaban or xarelto or apixaban or eliquis or edoxaban or lixiana or betrixaban or edoxaban or otamixaban).tw.<br>#9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8<br>#10 exp neoplasm/<br>#11 (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*).tw.<br>#12 10 or 11<br>#13 9 and 12<br>#14 crossover procedure/<br>#15 double-blind procedure/<br>#16 randomized controlled trial/<br>#17 single-blind procedure/<br>#18 random*.mp.<br>#19 factorial*.mp.<br>#20 (crossover* or cross over* or cross-over*).mp.<br>#21 placebo*.mp.<br>#22 (double* adj blind*).mp.<br>#23 (singl* adj blind*).mp.<br>#24 assign*.mp.<br>#25 allocat*.mp.<br>#26 volunteer*.mp.<br>#27 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26<br>#28 13 and 27<br>#29 (exp animal/ or nonhuman/ or exp animal experiment/) not human/<br>#30 28 not 29<br><br>Date limit: 01/2010 - 12/2013<br>Study Types: RCT | |
| **Records Retrieved: 733** | |

| Database: **Other** | |
|---|---|
| **Search strategy:** | **Date of search: 12/2013** |
| References of systematic reviews<br>Meeting Abstracts of American Society of clinical oncology<br>Meeting Abstracts of American Society of hematology<br><br>Date limit: 01/2010 - 12/2013<br>Study Types: RCT | |
| **Records Retrieved: 55** | |

| | |
|---|---|
| **Total No. Retrieved:** | **10088** |
| Cochrane: | 511 |
| Medline: | 602 |
| Embase: | 733 |
| Others: | 55 |
| OLD: | 8187 |
| **Duplicates:** | 529 |
| **No. Total** Without duplicates**:** | **9559** |
| **Screening** (Title and Abstract Review) | |
| No. Excluded | 9479 |
| Included for Full Text review: | 80 |
| **Selection** (Full Text Review): 13 (18 reports) | |
| No. Excluded: | 62 |
| Reasons for exclusions: | |
| • animal studies<br>• intervention different than a VKA<br>• by protocol,<br>• interventions were not similar among compared groups<br>• no relevant outcome<br>• duplicate publication<br>• study protocol<br>• letter to the editor<br>• abstracts later published in full and included in this review<br>• not a RCT<br>• review<br>• no outcome of interest<br>• no population of interest/ no cancer patients | |

4. **Should oral anticoagulation vs no oral anticoagulation be used in outpatients with cancer who have no other therapeutic or prophylactic indication for anticoagulation?**

| Database: **Cochrane Library** | |
|---|---|
| **Search strategy:** | **Date of search: 12/2013** |
| #1 MeSH descriptor: [Heparin] explode all trees | |

#2 (LMWH or heparin or nadroparin or fraxiparin or enoxaparin or clexane or lovenox or dalteparin or fragmin or ardeparin or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin or danaproid or orgaran or bemiparin or hibor, badyket, semuloparin, parnaparin, fluxum)
#3 MeSH descriptor: [Coumarins] explode all trees
#4 (warfarin or coumadin or acenocumarol or phenprocumon or 4-hydroxicoumarins or oral anticoagulant or vitamin K antagonist or VKA)
#5 (fondaparinux or arixtra)
#6 (ximelagatran or exanta)
#7 (pradaxa or dabigatran or rivaroxaban or xarelto or apixaban or eliquis or edoxaban or lixiana or betrixaban or edoxaban or otamixaban)
#8 #1 or #2 or #3 or #4 or #5 or #6 or #7
#9 MeSH descriptor: [Neoplasms] explode all trees
#10 (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*)
#11 #9 or #10
#12 #8 and #10

Date limit: 01/2010 - 12/2013
Study Types: RCT

| **Records Retrieved: 511** | |
|---|---|

Database: **MEDLINE**

| **Search strategy:** | **Date of search: 12/2013** |
|---|---|

#1 exp Heparin/
#2 (LMWH or heparin or nadroparin or fraxiparin or enoxaparin or clexane or lovenox or dalteparin or fragmin or ardeparin or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin or danaproid or orgaran or bemiparin or hibor, badyket, semuloparin, parnaparin, fluxum).tw.
#3 exp Coumarins/
#4 (warfarin or coumadin or acenocumarol or phenprocumon or 4-hydroxicoumarins or oral anticoagulant or vitamin K antagonist or VKA).tw.
#5 (fondaparinux or arixtra).tw.
#6 (ximelagatran or exanta).tw.
#7 (pradaxa or dabigatran or rivaroxaban or xarelto or apixaban or eliquis or edoxaban or lixiana or betrixaban or edoxaban or otamixaban).tw.
#8 1 or 2 or 3 or 4 or 5 or 6 or 7
#9 exp Neoplasms/
#10 (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*).tw.
#11 9 or 10
#12 8 and 11
#13 randomized controlled trial.pt.
#14 controlled clinical trial.pt.
#15 randomized.ab.
#16 placebo.ab.
#17 drug therapy.fs.
#18 randomly.ab.
#19 trial.ab.
#20 groups.ab.
#21 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
#22 12 and 21
#23 exp animals/ not humans.sh.
#24 22 not 23

Date limit: 01/2010 - 12/2013

| Study Types: RCT | |
|---|---|
| **Records Retrieved: 602** | |

| Database: **EMBASE** | |
|---|---|
| **Search strategy:** | **Date of search: 12/2013** |

#1 heparin/
#2 exp low molecular weight heparin/
#3 (LMWH or heparin or nadroparin or fraxiparin or enoxaparin or clexane or lovenox or dalteparin or fragmin or ardeparin or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin or danaproid or orgaran or bemiparin or hibor, badyket, semuloparin, parnaparin, fluxum).tw.
#4 exp coumarin derivative/
#5 (warfarin or coumadin or acenocumarol or phenprocumon or 4-hydroxicoumarins or oral anticoagulant or vitamin K antagonist or VKA).tw.
#6 (fondaparinux or arixtra).tw.
#7 (ximelagatran or exanta).tw.
#8 (pradaxa or dabigatran or rivaroxaban or xarelto or apixaban or eliquis or edoxaban or lixiana or betrixaban or edoxaban or otamixaban).tw.
#9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
#10 exp neoplasm/
#11 (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*).tw.
#12 10 or 11
#13 9 and 12
#14 crossover procedure/
#15 double-blind procedure/
#16 randomized controlled trial/
#17 single-blind procedure/
#18 random*.mp.
#19 factorial*.mp.
#20 (crossover* or cross over* or cross-over*).mp.
#21 placebo*.mp.
#22 (double* adj blind*).mp.
#23 (singl* adj blind*).mp.
#24 assign*.mp.
#25 allocat*.mp.
#26 volunteer*.mp.
#27 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
#28 13 and 27
#29 (exp animal/ or nonhuman/ or exp animal experiment/) not human/
#30 28 not 29

Date limit: 01/2010 - 12/2013
Study Types: RCT

| **Records Retrieved: 733** | |
|---|---|

| Database: **Other** | |
|---|---|
| **Search strategy:** | **Date of search: 12/2013** |

References of systematic reviews
Meeting Abstracts of American Society of clinical oncology
Meeting Abstracts of American Society of hematology

| | |
|---|---|
| Date limit: 01/2010 - 12/2013<br>Study Types: RCT | |
| **Records Retrieved: 55** | |

| | |
|---|---|
| **Total No. Retrieved:** | **10088** |
| Cochrane: | 511 |
| Medline: | 602 |
| Embase: | 733 |
| Others: | 55 |
| OLD: | 8187 |
| **Duplicates:** | 529 |
| **No Total** Without duplicates**:** | **9559** |
| **Screening** (Title and Abstract Review) | |
| No. Excluded | 9499 |
| Included for Full Text review: | 60 |
| **Selection** (Full Text Review): 7 ( 8 reports) | |
| No. Excluded | 52 |
| Reasons for exclusions: | |
| • animal studies<br>• intervention different than a VKA<br>• by protocol,<br>• interventions were not similar among compared groups<br>• no relevant outcome<br>• duplicate publication<br>• study protocol<br>• letter to the editor<br>• abstracts later published in full and included in this review<br>• not a RCT<br>• review<br>• no outcome of interest<br>• no population of interest/ no cancer patients | |

5. **Should parenteral anticoagulation vs no anticoagulation be used in patients with cancer and central venous catheters?**

**6. Should oral anticoagulation vs no anticoagulation be used in patients with cancer and central venous catheters?**

| Database: **Cochrane Library** | |
|---|---|
| **Search strategy:** | **Date of search: 12/2013** |
| #1 MeSH descriptor: [Heparin] explode all trees<br>#2 (LMWH or heparin or nadroparin or fraxiparin or enoxaparin or clexane or lovenox or dalteparin or fragmin or ardeparin or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin or danaproid or orgaran or bemiparin or hibor, badyket, semuloparin, parnaparin, fluxum)<br>#3 MeSH descriptor: [Coumarins] explode all trees<br>#4 (warfarin or coumadin or acenocumarol or phenprocumon or 4-hydroxicoumarins or oral anticoagulant or vitamin K antagonist or VKA)<br>#5 (fondaparinux or arixtra)<br>#6 (ximelagatran or exanta)<br>#7 (pradaxa or dabigatran or rivaroxaban or xarelto or apixaban or eliquis or edoxaban or lixiana or betrixaban or edoxaban or otamixaban)<br>#8 #1 or #2 or #3 or #4 or #5 or #6 or #7<br>#9 MeSH descriptor: [Neoplasms] explode all trees<br>#10 (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*)<br>#11 #9 or #10<br>#12 #8 and #10<br><br>Date limit: 01/2010 - 12/2013<br><br>Study Types: RCT | |
| **Records Retrieved: 511** | |

| Database: **MEDLINE** | |
|---|---|
| **Search strategy:** | **Date of search: 12/2013** |
| #1 exp Heparin/<br>#2 (LMWH or heparin or nadroparin or fraxiparin or enoxaparin or clexane or lovenox or dalteparin or fragmin or ardeparin or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin or danaproid or orgaran or bemiparin or hibor, badyket, semuloparin, parnaparin, fluxum).tw.<br>#3 exp Coumarins/<br>#4 (warfarin or coumadin or acenocumarol or phenprocumon or 4-hydroxicoumarins or oral anticoagulant or vitamin K antagonist or VKA).tw.<br>#5 (fondaparinux or arixtra).tw.<br>#6 (ximelagatran or exanta).tw.<br>#7 (pradaxa or dabigatran or rivaroxaban or xarelto or apixaban or eliquis or edoxaban or lixiana or betrixaban or edoxaban or otamixaban).tw.<br>#8 1 or 2 or 3 or 4 or 5 or 6 or 7<br>#9 exp Neoplasms/<br>#10 (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*).tw.<br>#11 9 or 10<br>#12 8 and 11<br>#13 randomized controlled trial.pt.<br>#14 controlled clinical trial.pt.<br>#15 randomized.ab.<br>#16 placebo.ab.<br>#17 drug therapy.fs.<br>#18 randomly.ab.<br>#19 trial.ab.<br>#20 groups.ab.<br>#21 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 | |

#22 12 and 21
#23 exp animals/ not humans.sh.
#24 22 not 23

Date limit: 01/2010 - 12/2013

Study Types: RCT

| **Records Retrieved: 602** | |
|---|---|

| Database: **EMBASE** | |
|---|---|
| **Search strategy:** | **Date of search: 12/2013** |

#1 heparin/
#2 exp low molecular weight heparin/
#3 (LMWH or heparin or nadroparin or fraxiparin or enoxaparin or clexane or lovenox or dalteparin or fragmin or ardeparin or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin or danaproid or orgaran or bemiparin or hibor, badyket, semuloparin, parnaparin, fluxum).tw.
#4 exp coumarin derivative/
#5 (warfarin or coumadin or acenocumarol or phenprocumon or 4-hydroxicoumarins or oral anticoagulant or vitamin K antagonist or VKA).tw.
#6 (fondaparinux or arixtra).tw.
#7 (ximelagatran or exanta).tw.
#8 (pradaxa or dabigatran or rivaroxaban or xarelto or apixaban or eliquis or edoxaban or lixiana or betrixaban or edoxaban or otamixaban).tw.
#9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
#10 exp neoplasm/
#11 (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*).tw.
#12 10 or 11
#13 9 and 12
#14 crossover procedure/
#15 double-blind procedure/
#16 randomized controlled trial/
#17 single-blind procedure/
#18 random*.mp.
#19 factorial*.mp.
#20 (crossover* or cross over* or cross-over*).mp.
#21 placebo*.mp.
#22 (double* adj blind*).mp.
#23 (singl* adj blind*).mp.
#24 assign*.mp.
#25 allocat*.mp.
#26 volunteer*.mp.
#27 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
#28 13 and 27
#29 (exp animal/ or nonhuman/ or exp animal experiment/) not human/
#30 28 not 29

Date limit: 01/2010 - 12/2013

Study Types: RCT

| **Records Retrieved: 733** | |
|---|---|

| Database: **Other** | |
|---|---|
| **Search strategy:** | **Date of search: 12/2013** |
| References of systematic reviews<br>Meeting Abstracts of American Society of clinical oncology<br>Meeting Abstracts of American Society of hematology<br><br>Date limit: 01/2010 - 12/2013<br><br>Study Types: RCT | |
| **Records Retrieved: 56** | |

| | |
|---|---|
| **Total No. Retrieved:** | **10089** |
| Cochrane: | 511 |
| Medline: | 602 |
| Embase: | 733 |
| Others: | 56 |
| OLD: | 8187 |
| **Duplicates:** | 529 |
| **No. Total** Without duplicates**:** | 9560 |
| **Screening** (Title and Abstract review) | |
| No. Excluded: | 9518 |
| Included for Full Text review: | 42 |
| **Selection** (Full Text Review): 13 | |
| No. Excluded : | 29 |
| Reasons for exclusions: | |
| • Not population of interest<br>• Not intervention of interest<br>• Differential follow-up relative to randomization<br>• Not an RCT<br>• Intervention was compared to urokinase<br>• No data available for the subgroup of cancer patients | |

7. **Should Low Molecular Weight Heparin (LMWH) vs Unfractionated Heparin (UFH) be used in patients with cancer being initiated on treatment for venous thromboembolism?**

| Database: **Cochrane Library** | |
|---|---|
| **Search strategy:** | **Date of search: 12/2013** |
| #1 MeSH descriptor: [Heparin] explode all trees<br>#2 (LMWH or heparin or nadroparin or fraxiparin or enoxaparin or clexane or lovenox or dalteparin or fragmin or ardeparin or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin or danaproid or orgaran or bemiparin or hibor, badyket, semuloparin, parnaparin, fluxum)<br>#3 MeSH descriptor: [Coumarins] explode all trees<br>#4 (warfarin or coumadin or acenocumarol or phenprocumon or 4-hydroxicoumarins or oral anticoagulant or vit- | |

amin K antagonist or VKA)
#5 (fondaparinux or arixtra)
#6 (ximelagatran or exanta)
#7 (pradaxa or dabigatran or rivaroxaban or xarelto or apixaban or eliquis or edoxaban or lixiana or betrixaban or edoxaban or otamixaban)
#8 #1 or #2 or #3 or #4 or #5 or #6 or #7
#9 MeSH descriptor: [Neoplasms] explode all trees
#10 (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*)
#11 #9 or #10
#12 #8 and #10

Date limit: 01/2010 - 12/2013
Study Types: RCT

| **Records Retrieved: 511** | |
|---|---|

Database: **MEDLINE**

| **Search strategy:** | **Date of search: 12/2013** |
|---|---|

#1 exp Heparin/
#2 (LMWH or heparin or nadroparin or fraxiparin or enoxaparin or clexane or lovenox or dalteparin or fragmin or ardeparin or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin or danaproid or orgaran or bemiparin or hibor, badyket, semuloparin, parnaparin, fluxum).tw.
#3 exp Coumarins/
#4 (warfarin or coumadin or acenocumarol or phenprocumon or 4-hydroxicoumarins or oral anticoagulant or vit-amin K antagonist or VKA).tw.
#5 (fondaparinux or arixtra).tw.
#6 (ximelagatran or exanta).tw.
#7 (pradaxa or dabigatran or rivaroxaban or xarelto or apixaban or eliquis or edoxaban or lixiana or betrixaban or edoxaban or otamixaban).tw.
#8 1 or 2 or 3 or 4 or 5 or 6 or 7
#9 exp Neoplasms/
#10 (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*).tw.
#11 9 or 10
#12 8 and 11
#13 randomized controlled trial.pt.
#14 controlled clinical trial.pt.
#15 randomized.ab.
#16 placebo.ab.
#17 drug therapy.fs.
#18 randomly.ab.
#19 trial.ab.
#20 groups.ab.
#21 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
#22 12 and 21
#23 exp animals/ not humans.sh.
#24 22 not 23

Date limit: 01/2010 - 12/2013
Study Types: RCT

| **Records Retrieved: 602** | |
|---|---|

| Database: **EMBASE** | |
|---|---|
| **Search strategy:** | **Date of search: 12/2013** |
| #1 heparin/<br>#2 exp low molecular weight heparin/<br>#3 (LMWH or heparin or nadroparin or fraxiparin or enoxaparin or clexane or lovenox or dalteparin or fragmin or ardeparin or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin or danaproid or orgaran or bemiparin or hibor, badyket, semuloparin, parnaparin, fluxum).tw.<br>#4 exp coumarin derivative/<br>#5 (warfarin or coumadin or acenocumarol or phenprocumon or 4-hydroxicoumarins or oral anticoagulant or vitamin K antagonist or VKA).tw.<br>#6 (fondaparinux or arixtra).tw.<br>#7 (ximelagatran or exanta).tw.<br>#8 (pradaxa or dabigatran or rivaroxaban or xarelto or apixaban or eliquis or edoxaban or lixiana or betrixaban or edoxaban or otamixaban).tw.<br>#9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8<br>#10 exp neoplasm/<br>#11 (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*).tw.<br>#12 10 or 11<br>#13 9 and 12<br>#14 crossover procedure/<br>#15 double-blind procedure/<br>#16 randomized controlled trial/<br>#17 single-blind procedure/<br>#18 random*.mp.<br>#19 factorial*.mp.<br>#20 (crossover* or cross over* or cross-over*).mp.<br>#21 placebo*.mp.<br>#22 (double* adj blind*).mp.<br>#23 (singl* adj blind*).mp.<br>#24 assign*.mp.<br>#25 allocat*.mp.<br>#26 volunteer*.mp.<br>#27 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26<br>#28 13 and 27<br>#29 (exp animal/ or nonhuman/ or exp animal experiment/) not human/<br>#30 28 not 29<br><br>Date limit: 01/2010 - 12/2013<br>Study Types: RCT | |
| **Records Retrieved: 733** | |

| Database: **Other** | |
|---|---|
| **Search strategy:** | **Date of search: 12/2013** |
| References of systematic reviews<br>Meeting Abstracts of American Society of clinical oncology<br>Meeting Abstracts of American Society of hematology<br><br>Date limit: 01/2010 - 12/2013<br>Study Types: RCT | |
| **Records Retrieved: 55** | |

| | |
|---|---|
| **Total No. Retrieved:** | **10088** |
| Cochrane: | 511 |
| Medline: | 602 |
| Embase: | 733 |
| Others: | 55 |
| OLD: | 8187 |
| **Duplicates:** | 529 |
| **No. Total** Without duplicates**:** | **9559** |
| **Screening** (Title and Abstract Review) | |
| No. Excluded: | 9500 |
| Included for Full Text review: | 59 |
| **Selection** (Full Text Review): 16 ( 18 reports) | |
| No. Excluded | 43 |
| Reasons for exclusions: | |
| • No outcome data available for cancer study subgroups<br>• review<br>• case report or series<br>• letter to the editor or editorial<br>• cohort study<br>• no patients with cancer included<br>• retrospective study<br>• no relevant outcome<br>• different long-term management<br>• not randomized<br>• survey | |

8. **Should heparin vs oral anticoagulation be used in patients with cancer requiring long term treatment of venous thromboembolism?**

| Database: **Cochrane Library** | |
|---|---|
| **Search strategy:** | **Date of search: 12/2013** |
| #1 MeSH descriptor: [Heparin] explode all trees<br>#2 (LMWH or heparin or nadroparin or fraxiparin or enoxaparin or clexane or lovenox or dalteparin or fragmin or ardeparin or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin or danaproid or orgaran or bemiparin or hibor, badyket, semuloparin, parnaparin, fluxum)<br>#3 MeSH descriptor: [Coumarins] explode all trees<br>#4 (warfarin or coumadin or acenocumarol or phenprocumon or 4-hydroxicoumarins or oral anticoagulant or vitamin K antagonist or VKA)<br>#5 (fondaparinux or arixtra)<br>#6 (ximelagatran or exanta)<br>#7 (pradaxa or dabigatran or rivaroxaban or xarelto or apixaban or eliquis or edoxaban or lixiana or betrixaban or edoxaban or otamixaban)<br>#8 #1 or #2 or #3 or #4 or #5 or #6 or #7<br>#9 MeSH descriptor: [Neoplasms] explode all trees<br>#10 (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*) | |

| |
|---|
| #11 #9 or #10<br>#12 #8 and #10<br><br>Date limit: 01/2010 - 12/2013<br>Study Types: RCT |
| **Records Retrieved: 511** |

| Database: **MEDLINE** | |
|---|---|
| **Search strategy:** | **Date of search: 12/2013** |
| #1 exp Heparin/<br>#2 (LMWH or heparin or nadroparin or fraxiparin or enoxaparin or clexane or lovenox or dalteparin or fragmin or ardeparin or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin or danaproid or orgaran or bemiparin or hibor, badyket, semuloparin, parnaparin, fluxum).tw.<br>#3 exp Coumarins/<br>#4 (warfarin or coumadin or acenocumarol or phenprocumon or 4-hydroxicoumarins or oral anticoagulant or vitamin K antagonist or VKA).tw.<br>#5 (fondaparinux or arixtra).tw.<br>#6 (ximelagatran or exanta).tw.<br>#7 (pradaxa or dabigatran or rivaroxaban or xarelto or apixaban or eliquis or edoxaban or lixiana or betrixaban or edoxaban or otamixaban).tw.<br>#8 1 or 2 or 3 or 4 or 5 or 6 or 7<br>#9 exp Neoplasms/<br>#10 (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*).tw.<br>#11 9 or 10<br>#12 8 and 11<br>#13 randomized controlled trial.pt.<br>#14 controlled clinical trial.pt.<br>#15 randomized.ab.<br>#16 placebo.ab.<br>#17 drug therapy.fs.<br>#18 randomly.ab.<br>#19 trial.ab.<br>#20 groups.ab.<br>#21 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20<br>#22 12 and 21<br>#23 exp animals/ not humans.sh.<br>#24 22 not 23<br><br>Date limit: 01/2010 - 12/2013<br>Study Types: RCT | |
| **Records Retrieved: 602** | |

| Database: **EMBASE** | |
|---|---|
| **Search strategy:** | **Date of search: 12/2013** |
| #1 heparin/<br>#2 exp low molecular weight heparin/<br>#3 (LMWH or heparin or nadroparin or fraxiparin or enoxaparin or clexane or lovenox or dalteparin or fragmin or ardeparin or normiflo or tinzaparin or logiparin or innohep or certoparin or sandoparin or reviparin or clivarin or danaproid or orgaran or bemiparin or hibor, badyket, semuloparin, parnaparin, fluxum).tw.<br>#4 exp coumarin derivative/ | |

#5 (warfarin or coumadin or acenocumarol or phenprocumon or 4-hydroxicoumarins or oral anticoagulant or vitamin K antagonist or VKA).tw.
#6 (fondaparinux or arixtra).tw.
#7 (ximelagatran or exanta).tw.
#8 (pradaxa or dabigatran or rivaroxaban or xarelto or apixaban or eliquis or edoxaban or lixiana or betrixaban or edoxaban or otamixaban).tw.
#9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
#10 exp neoplasm/
#11 (malignan* or neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*).tw.
#12 10 or 11
#13 9 and 12
#14 crossover procedure/
#15 double-blind procedure/
#16 randomized controlled trial/
#17 single-blind procedure/
#18 random*.mp.
#19 factorial*.mp.
#20 (crossover* or cross over* or cross-over*).mp.
#21 placebo*.mp.
#22 (double* adj blind*).mp.
#23 (singl* adj blind*).mp.
#24 assign*.mp.
#25 allocat*.mp.
#26 volunteer*.mp.
#27 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
#28 13 and 27
#29 (exp animal/ or nonhuman/ or exp animal experiment/) not human/
#30 28 not 29

Date limit: 01/2010 - 12/2013
Study Types: RCT

| **Records Retrieved: 733** | |
|---|---|

Database: **Other**

| **Search strategy:** | **Date of search: 12/2013** |
|---|---|

References of systematic reviews
Meeting Abstracts of American Society of clinical oncology
Meeting Abstracts of American Society of hematology

Date limit: 01/2010 - 12/2013
Study Types: RCT

| **Records Retrieved: 55** | |
|---|---|

| | |
|---|---|
| **Total No. Retrieved:** | **10088** |
| Cochrane: | 511 |
| Medline: | 602 |
| Embase: | 733 |
| Others: | 55 |
| OLD: | 8187 |
| **Duplicates:** | 529 |
| **No. Total** Without duplicates**:** | **9559** |
| **Screening** (Title and Abstract Review) | |
| No. Excluded: | 9494 |
| Included for Full Text review: | 65 |
| **Selection** (Full Text Review): 10 ( 11 reports) | |
| No. Excluded: | 54 |
| Reasons for exclusions: | |
| • patients with cancer constituted study subgroups but their outcome data were not available<br>• case series<br>• review (n=15),<br>• retrospective study<br>• protocol<br>• observational study<br>• trial but not randomized and controlled<br>• no cancer patients included<br>• only one patient with cancer was included<br>• no relevant outcome<br>• not intervention of interest<br>• study compares different duration of interventional drugs | |


المركز السعودي للرعاية الصحية المبنية على البراهين
The Saudi Center for Evidence Based Health Care
وزارة الصحة
Ministry of Health