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Evidence Based Health Care

Stroke

Clinical Practice Guideline on Prevention of Venous Thromboembolism in Patients with Stroke

April 2014

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Contents

Executive summary

Introduction

Patients with stroke and restricted mobility are at risk of developing venous thromboembolism (VTE). VTE after stroke is associated with significant morbidity and mortality. Given the importance of this condition, the Ministry of Health (MoH) of the Kingdom of Saudi Arabia (KSA) 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.

Methodology

This clinical practice guideline is a part of the larger initiative of the Ministry of Health 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 and Thrombolytic Therapy for Ischemic Stroke" chapter of the 2012 Antithrombotic Therapy and Prevention of Thrombosis guidelines, 9th edition (see **Appendix 1**).[1] 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.[2] We used this information to prepare the evidence to recommendation tables that served the guideline panel to follow the structured consensus process and transparently document all decisions made during the meeting (see **Appendix 2**). 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.[3]

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.[4] 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 low dose heparin (unfractionated heparin [UFH] or low molecular weight heparin [LMWH]) be used in patients with acute ischemic stroke and restricted mobility for VTE prevention, when compared to no prophylaxis?
2. Should low dose LMWH be used in patients with acute ischemic stroke and restricted mobility for VTE prevention, when compared to low dose UFH?
3. Should intermittent pneumatic compression (IPC) be used in patients with acute ischemic stroke and restricted mobility for VTE prevention, when compared to no IPC?
4. Should elastic compression stocking be used in patients with acute ischemic stroke and restricted mobility for VTE prevention when compared to no prophylaxis?
5. Should low dose heparin (UFH or LMWH) be used in patients with hemorrhagic stroke and restricted mobility for VTE prevention, when compared to no prophylaxis?
6. Should early (day 2) heparin prophylaxis be recommended in patients with hemorrhagic stroke and restricted mobility when compared to late (day 4) heparin prophylaxis?
7. Should low dose LMWH be used in patients with hemorrhagic stroke and restricted mobility for VTE prevention, when compared to low dose UFH?
8. Should IPC be used in patients with hemorrhagic stroke and restricted mobility for VTE prevention, when compared to no IPC?

Recommendations

Recommendation 1:
The KSA MoH panel recommends using prophylactic dose heparin in patients with acute ischemic stroke and restricted mobility (strong recommendation, moderate quality of evidence).

Remark:
Starting prophylactic dose heparin should be delayed for 24 hours in patients who received thrombolytic therapy.

Recommendation 2:
The KSA MoH panel suggests using prophylactic dose LMWH over UFH in patients with acute ischemic stroke and restricted mobility. (Weak recommendation, moderate quality of evidence).

Recommendation 3:
The KSA MoH panel recommends using IPC in patients with acute ischemic stroke and restricted mobility. (Strong recommendation, moderate quality of evidence).

Remark:
IPC should be considered in patients who cannot receive prophylactic low dose heparin, and should be avoided in patients who have peripheral vascular disease.

Recommendation 4:
The KSA MoH panel suggests against using elastic compression stocking for VTE prevention in patients with ischemic stroke and restricted mobility (Weak recommendation, moderate quality of evidence).

Recommendation 5:
The KSA MoH panel suggests using prophylactic dose heparin in patients with hemorrhagic stroke and restricted mobility. (Weak recommendation, low quality of evidence).

Recommendation 6:
The KSA MoH panel suggests early (within days 2 to 4) use of prophylactic dose heparin for VTE prevention in patients with hemorrhagic stroke and restricted mobility. (Weak recommendation, very low quality of evidence).

Recommendation 7:
The KSA MoH panel suggests using prophylactic dose LMWH over UFH in patients with hemorrhagic stroke and restricted mobility. (Weak recommendation, very low quality of evidence).

Remark:
Very low quality of evidence suggests that the use of LMWH or UFH may be safe in patients with hemorrhagic stroke. However, comparative studies in this population are lacking.

Recommendation 8:
The KSA MoH panel suggests using IPC in patients with hemorrhagic stroke and restricted mobility over no prophylaxis. (Weak recommendation, low quality of evidence).

Scope and purpose

The purpose of this document is to provide guidance about the prevention of venous thromboembolism in patients with stroke. The target audience of these guidelines includes neurologists, specialists in internal medicine, and hospitalists in the Kingdom of Saudi Arabia. Primary care physicians, critical care specialists, other health care professionals 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

Patients with stroke and restricted mobilization are at risk of developing venous thromboembolism (VTE)[5]. VTE post stroke is associated with significant morbidity and mortality[6]. There are no studies from the Kingdom of Saudi Arabia (KSA) that describe the prognosis or prevalence of this condition. Dennis et al. conducted an observational study that used duplex ultrasound to screen 5632 patients from the first and second CLOTS trials[7]. Within the first 8 days after a stroke, the prevalence of deep venous thrombosis (DVT) and pulmonary embolism (PE) were 11% and 5%, respectively. Additional 3% developed DVT at 28 days. Furthermore, it is estimated that PE account for 13 to 24% of early deaths after stroke usually occurring in the fourth week but can occur earlier[6]. These studies illustrate the importance of implementing VTE preventive strategies early after a stroke event. Given the importance of this topic, the Ministry of Health (MoH) 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.

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.[8]

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 and Thrombolytic Therapy for Ischemic Stroke" chapter of the 2012 Antithrombotic Therapy and Prevention of Thrombosis guidelines, 9th edition (see **Appendix 1**).[1] 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 (see **Appendix 2**).[2]

We assessed the quality of evidence using the system described by the GRADE working group.[4] 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.

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

Based on this information and the input of KSA MoH panel members we prepared the evidence-to-recommendation tables that served the guideline panel to follow the structured consensus process and transparently document all decisions made during the meeting (see **Appendix 2**). 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.[3]

How to use these guidelines

The Ministry of Health of Saudi Arabia and McMaster University Clinical Practice Guidelines provide clinicians and their patients with a basis for rational decisions in the management of ischemic stroke. Clinicians, patients, third-party payers, institutional review committees, other stakeholders, or the courts should never view these recommendations as dictates. No guidelines and 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.

Statements about the underlying values and preferences as well as 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.[8]

1. Should low dose heparin (unfractionated heparin [UFH] or low molecular weight heparin [LMWH]) be used in patients with acute ischemic stroke and restricted mobility for VTE prevention, when compared to no prophylaxis?
2. Should low dose LMWH be used in patients with acute ischemic stroke and restricted mobility for VTE prevention, when compared to low dose UFH?
3. Should intermittent pneumatic compression (IPC) be used in patients with acute ischemic stroke and restricted mobility for VTE prevention, when compared to no IPC?
4. Should elastic compression stocking be used in patients with acute ischemic stroke and restricted mobility for VTE prevention when compared to no prophylaxis?
5. Should low dose heparin (UFH or LMWH) be used in patients with hemorrhagic stroke and restricted mobility for VTE prevention, when compared to no prophylaxis?
6. Should early (day 2) heparin prophylaxis be recommended in patients with hemorrhagic stroke and restricted mobility when compared to late (day 4) heparin prophylaxis?

7. Should low dose LMWH be used in patients with hemorrhagic stroke and restricted mobility for VTE prevention, when compared to low dose UFH?
8. Should IPC be used in patients with hemorrhagic stroke and restricted mobility for VTE prevention, when compared to no IPC?

Recommendations

I. Prophylactic dose heparin in patients with ischemic stroke:

Question 1: Should prophylactic dose heparin (UFH or LMWH) be used in patients with acute ischemic stroke and restricted mobility for VTE prevention, when compared to no prophylaxis?

Summary of findings:
A systematic review[9] that included data from eight randomized controlled trials (RCTs)[10-15] showed that the use of prophylactic dose heparin reduces symptomatic DVT (30 fewer DVTs per 1000 treated patients), and may reduce the risk of PE however the effect on PE ranged from 8 fewer events to no difference. The effect on mortality and bleeding outcomes was uncertain [Table 2].

Values and preferences:
There are no published data on values and preferences in the context of the KSA.

Cost effectiveness:
There are no published or unpublished data on the cost effectiveness of heparin prophylaxis in the context of Saudi Arabia.

Other considerations:
Timing of initiation of prophylactic dose heparin in patients who received thrombolytic therapy is not clear. The use of prophylactic dose heparin should be delayed for 24 hours in patients receiving thrombolytic therapy due to risk of bleeding[9]. Prophylactic dose heparin is defined as 10,000 to 15,000 units/day for UFH, and 3000 to 5000 international units/day for LMWH[9].**Recommendation 1:**

The KSA MoH panel recommends using prophylactic dose heparin in patients with acute ischemic stroke and restricted mobility (strong recommendation, moderate quality of evidence).

Remark:
Starting prophylactic dose heparin should be delayed for 24 hours in patients who received thrombolytic therapy.

Question 2: Should low dose LMWH be used in patients with acute ischemic stroke and restricted mobility for VTE prevention, when compared to low dose UFH?

Summary of findings:
A systematic review[16] that included 3 RCTs[17-19] showed that the use of prophylactic dose LMWH is associated with lower risk of symptomatic DVT and PE; that translate to 7 fewer DVTs per 1000 treated patients and 8 fewer PEs per 1000 treated patients [Table 3]. The effect on mortality, intracranial and extracranial bleeding was uncertain. The quality of evidence was moderate for all outcomes; hence the overall quality of evidence is moderate [Table 3]. We did not identify new RCTs or systematic review.

Values and preferences:
There are no published data on values and preferences in the context of the KSA.

Cost effectiveness:
There are no published or unpublished data on the cost effectiveness of heparin prophylaxis in the context of Saudi Arabia.

Recommendation 2:

The KSA MoH panel suggests using prophylactic dose LMWH over UFH in patients with acute ischemic stroke and restricted mobility. (Weak recommendation, moderate quality of evidence).

II. Mechanical VTE prophylaxis in patients with ischemic stroke:

Question 3: Should IPC be used in patients with acute ischemic stroke and restricted mobility for VTE prevention, when compared to no IPC?

Summary of findings:
The updated search identified a new RCT (CLOTS 3)[20] that contributed to all outcomes of interest. When pooling the results of three RCTs, there was uncertainty about mortality outcome[20]. The absolute risk difference ranged between 42 fewer deaths to one more death per 1000 treated patients [Table 4]. Only CLOTS 3 reported the risk of symptomatic DVT and PE. The use of IPC resulted in lower risk of symptomatic DVT (RR 0.73; 95% CI 0.53 to 0.99) but not PE (RR 0.83; 95% CI 0.51 to 1.35). The overall quality of evidence is moderate. Patients with peripheral vascular disease were excluded from CLOTS 3 to avoid worsening pre-existing chronic ischemia.

Prophylactic low dose heparin was not directly compared to IPC in clinical trials. However, the effect size was larger when comparing heparin prophylaxis to no prophylaxis (RR 0.38; 95% CI 0.21 to 0.70).

Values and preferences:
There are no published data on values and preferences in the context of the KSA.

Cost effectiveness:
There are no published or unpublished data on the cost effectiveness of IPC for VTE prevention in the context of Saudi Arabia.

Recommendation 3:

The KSA MoH panel recommends using IPC in patients with acute ischemic stroke and restricted mobility. (Strong recommendation, moderate quality of evidence).

Remark:
IPC should be considered in patients who cannot receive prophylactic low dose heparin, and should be avoided in patients who have peripheral vascular disease.

Question 4: Should elastic compression stocking be used in patients with acute ischemic stroke and restricted mobility for VTE prevention when compared to no prophylaxis?

Elastic compression stocking (graduate compression stocking) are stocking designed to apply pressure on the lower limbs with different gradient being higher distally than proximally. The end result is increase in the venous return, theoretically preventing DVT formation.

Summary of findings:
We did not identify new RCTs or systematic reviews. Two RCTs[21,22] (N=2651) examined the effect of elastic compression stocking on mortality compared to no prophylaxis. Pooling the results of these RCTs, there was uncertainty about the risk of death (RR 1.11; 95% CI 0.88 to 1.42). Only one RCT (N=2518) reported other critical outcomes[22]. The use of elastic compression stocking did not significantly reduce the risk of symptomatic DVT (RR 0.91; 95%CI 0.63 to 1.29), or PE (RR 0.65; 95%CI 0.33 to 1.31) compared to no prophylaxis. However, it resulted in higher risk of skin complications (RR 4.02; 95%CI 2.34 to 6.91) that translates to an absolute risk increase of 39 per 1000 treated patients. The overall quality of evidence is moderate mainly due to imprecision and risk of bias [Table 5].

Values and preferences:
There are no published data on values and preferences in the context of the KSA.

Cost effectiveness:
There are no published or unpublished data on the cost effectiveness of elastic stockings for VTE prevention in the context of Saudi Arabia.

Recommendation 4:

The KSA MoH panel suggests against using elastic compression stocking for VTE prevention in patients with ischemic stroke and restricted mobility (Weak recommendation, moderate quality of evidence).

III. Prophylactic dose heparin in patients with hemorrhagic stroke:

Question 5: Should low dose heparin (UFH or LMWH) be used in patients with hemorrhagic stroke and restricted mobility for VTE prevention, when compared to no prophylaxis?

Summary of findings:
The evidence from studies conducted in ischemic stroke population was of higher quality than studies in hemorrhagic stroke population; therefore we used indirect higher quality evidence for DVT and PE outcomes. Our updated search did not identify new studies.

Two small RCTs[23,24] with a total of 114 patients reported mortality in hemorrhagic stroke population. The results were imprecise to conclude benefit or harm (RR 1.05; 95% CI, 0.48-2.36). One study compared LMWH to compression stocking and was not included in this analysis[25]. The quality of evidence for mortality outcome is low due to risk of bias and imprecision [Table 6]. For symptomatic DVT and PE we used indirect evidence from studies conducted in ischemic stroke population, the use of prophylactic dose heparin reduces symptomatic DVT (30 fewer DVTs per 1000 treated patients), and may reduce the risk of PE however the effect on PE ranged from 8 fewer events to no difference. The quality of evidence is moderate for PE outcome and low for symptomatic DVT outcome, we did not lower quality of evidence for indirectness [Table 6].

Three small RCTs (n=189) reported rebleeding in patients with intracranial hemorrhage (ICH) receiving prophylactic dose heparin[23-25]. The use of low dose heparin did not significantly increase the risk of rebleeding; on average there were 8 fewer rebleeding events per 1000 treated patients (95% CI 9 fewer to 1 more per 1000). However, the results are imprecise due to small sample size, and studies were at high risk of bias. Hence, the quality of evidence for this outcome was judged to be low and the overall quality of evidence across all critical outcomes is low [Table 6].

Values and preferences:
There are no published data on values and preferences in the context of the KSA.

Recommendation 5:

The KSA MoH panel suggests using prophylactic dose heparin in patients with hemorrhagic stroke and restricted mobility. (Weak recommendation, low quality of evidence).

Question 6: Should early (day 2) heparin prophylaxis be recommended in patients with hemorrhagic stroke and restricted mobility when compared to late (day 4) heparin prophylaxis?

Summary of findings:
Updated search did not identify new studies. A small RCT (n=45) compared early (day 2 after admission) to late (day 4 after admission) start of prophylactic dose UFH in patients with hemorrhagic stroke[23]. This study was designed to randomize patients to receive heparin prophylaxis at days 4 and 10 after admission. A third group (non-randomized) was added in which patients received heparin at day 2 after admission. The sample size is too small to make any conclusions regarding mortality, DVT, PE, and rebleeding outcomes [Table 7]. However, there was only one rebleeding event that occurred in the late group compared to no events in the early group; this provides a very low quality of evidence about the safety of early use of low dose heparin.
The overall quality of evidence is very low due to imprecision and risk of bias for most outcomes [Table 7]. Another RCT randomized patients with ICH (at day 2) to receive either prophylactic dose LMWH or IPC; there were no rebleeding events in both groups at 21 days of follow up[25].
Although the early use of prophylactic heparin appears to be safe, a large RCT is warranted to inform future guidelines.

Values and preferences:
There are no published data on values and preferences in the context of the KSA.

Recommendation 6:

The KSA MoH panel suggests early (within days 2 to 4) use of prophylactic dose heparin for VTE prevention in patients with hemorrhagic stroke and restricted mobility. (Weak recommendation, very low quality of evidence).

Question 7: Should low dose LMWH be used in patients with hemorrhagic stroke and restricted mobility for VTE prevention, when compared to low dose UFH?

Summary of findings:
LMWH and UFH were not directly compared in the hemorrhagic stroke population. We used indirect evidence from ischemic stroke population to inform this recommendation [Table 3]. Hence, we lowered quality of evidence for indirectness. It is unknown if the

risk of VTE is significantly different between both population, however the efficacy of the intervention is likely to be similar. Until new evidence is available we believe it is reasonable to generalize the results to the hemorrhagic stroke population. The risk of symptomatic intracranial bleeding was not significantly changed in ischemic stroke population [Table 3]. A small RCT (n=75) comparing LMWH to compression stockings in patients with primary ICH did not show any rebleeding events at 21 days[25]. We used indirect evidence on the use of heparin prophylaxis in patients with hemorrhagic stroke [Table 6]. This provides very low quality of evidence on the safety of using UFH and LMWH in patients with hemorrhagic stroke. We lowered the quality of evidence due to indirectness.

Values and preferences:
There are no published data on values and preferences in the context of the KSA.

Recommendation 7:

The KSA MoH panel suggests using prophylactic dose LMWH over UFH in patients with hemorrhagic stroke and restricted mobility. (Weak recommendation, very low quality of evidence).

Remark:
Very low quality of evidence suggests that the use of LMWH or UFH may be safe in patients with hemorrhagic stroke. However, comparative studies in this population are lacking.

IV. Mechanical VTE prevention in patients with hemorrhagic stroke:

Question 8: Should IPC be used in patients with hemorrhagic stroke and restricted mobility for VTE prevention, when compared to no IPC?

Summary of findings:
There are no RCTs comparing IPC to no prophylaxis exclusively in patients with hemorrhagic stroke. In CLOTS 3 patients with stroke were randomized to receive IPC or no prophylaxis. A subgroup analysis looking at patients with hemorrhagic stroke showed that the use of IPC reduces the risk of proximal DVT (OR=0.36; 95%CI 0.17 to 0.75)[20]. The study did not report mortality, symptomatic DVT or PE outcomes in hemorrhagic stroke subgroup. Therefore, we used indirect evidence looking at acute stroke patients (11% with hemorrhagic stroke) from the same study [Table 4]. The effect of IPC on rebleeding outcome is unknown; few studies in different population showedthat IPC use may increase fibrinolytic activity,[26,27] while other studies did not show increased fibrinolytic activity.[28-30] It is not clear if these observations translate into clinical outcomes. We lowered the quality of evidence for indirectness; the overall quality of evidence is low.

Values and preferences:
There are no published data on values and preferences in the context of the KSA.

Recommendation 8:

The KSA MoH panel suggests using IPC in patients with hemorrhagic stroke and restricted mobility. (Weak recommendation, low quality of evidence).

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Appendices

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

Appendix 1: Search Strategies and Results

Databases: Medline and Cochrane Library	
Search strategy:	Date of search: 2013-10-19

1. exp Intracranial Hemorrhages/
2. exp *Brain Ischemia/
3. exp *"intracranial embolism and thrombosis"/ or exp *intracranial hemorrhages/ or exp *stroke/ or exp *brain infarction/
4. exp *Heparin/ or exp *Heparin, Low-Molecular-Weight/
5. exp *Stockings, Compression/
6. exp *Heparinoids/
7. exp *embolectomy/ or exp *thrombectomy/
8. intermittent Pneumatic Compression Stockings.mp.
9. *Fibrinolytic Agents/tu [Therapeutic Use]
10. *Thrombolytic Therapy/mt [Methods]
11. *Tissue Plasminogen Activator/tu [Therapeutic Use]
12. bandages/ or stockings, compression/
13. exp Anticoagulants/
14. Intermittent Pneumatic Compression Devices/
15. 1 or 2 or 3
16. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
17. 15 and 16
18. limit 17 to (english language and humans and yr="2012 -Current")
19. (MEDLINE or metaanaly$ or meta-analy$ or (systemat$ adj10 review$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
20. limit 18 to (case reports or clinical conference or comment or congresses or editorial or in vitro or letter)
21. 18 not 20
22. 21 and 19
23. randomised controlled trial.pt.
24. controlled clinical trial.pt.
25. random$.ab.
26. trial.ab.
27. groups.ab.
28. 23 or 24 or 25 or 26 or 27
29. 21 and 28

Date: 2012 – 2013-10-19

Summary of Searches

Total No. Retrieved:	671
Cochrane:	274
Medline:	397
Screening (Title and Abstract Review)	
No. Excluded:	667
Included for Full Text review:	4
Selection (Full Text Review)	
No. Excluded:	2
Reasons for exclusions:	
1. Protocol (1) 2. Different interventions (1)	
No. Selected:	2
1. RCT (1) 2. SR (1)	

Appendix 2: Summary of Findings and Evidence-to-Recommendation Tables

Table 2
Summary of Findings: Prophylactic dose heparin (LMWH or UFH) compared to no prophylactic low dose anticoagulation in patients with acute ischemic stroke and restricted mobility

Prophylactic dose heparin (LMWH or UFH) compared to no prophylactic low dose anticoagulation in patients with acute ischemic stroke and restricted mobility

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk		Relative effect (95% CI)	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)
	Risk with No prophylactic low dose anticoagulation	Risk difference with Prophylactic low dose heparin (UFH or LMWH)			
Mortality	**87 deaths per 1000**[2,3]	**12 fewer per 1000** (from 36 fewer to 19 more)	**RR 0.86** (0.59 to 1.22)	15594 (8 studies[4]) 30 days[5]	⊕⊕⊕◯ **MODERATE**[6,7] due to imprecision
Pulmonary Embolism	**16 PEs per 1000**[8]	**5 fewer per 1000** (from 8 fewer to 0 more)	**RR 0.7** (0.47 to 1.03)[8]	10681 (8 studies) 30 days	⊕⊕⊕◯ **MODERATE**[6,7,9] due to imprecision
Symptomatic DVT	**48 DVTs per 1000**[2]	**30 fewer per 1000** (from 38 fewer to 14 fewer)	**RR 0.38** (0.21 to 0.70)	914 (8 studies) 30 days	⊕⊕◯◯ **MODERATE**[6,10] due to inconsistency
Symptomatic intra-cranial hemorrhage	**5 bleeding events per 1000**	**3 more per 1000** (from 0 fewer to 7 more)	**RR 1.52** (0.96 to 2.39)	10696 (5 studies) 30 days[5]	⊕⊕⊕◯ **MODERATE**[6,7,9] due to imprecision
Symptomatic extra-cranial hemorrhage	**4 bleeding events per 1000**	**2 more per 1000** (from 0 fewer to 7 more)	**RR 1.62** (0.93 to 2.81)	10351 (5 studies) 30 days[5]	⊕⊕⊕◯ **MODERATE**[6,7,9] due to imprecision

*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] Data on the concomitant use of aspirin were generally insufficiently provided. In most studies, like the IST, aspirin use was permitted, but exact numbers of patients using antiplatelet agents were lacking.

[2] Control rate derived from CLOTS trial judged to provide the most representative estimates of baseline risk in the population of patients with stroke and limited mobility.
[3] IST data: since "there was no interaction between aspirin and heparin in the main outcomes", we combined data from patients with and without aspirin in the low heparin group (2432+ 2426=4858) and data from patients with and without aspirin in the no heparin group (4858+ 4860=9718)
[4] Death from bleeding occurred in 0.55% of 4860 patients on low dose heparin and 0.21% of 10176 control patients (RR 2.68; 95% CI 1.5-4.7). Absolute effect equals 3 more per 1000 (from 1 more to 7 more). Data is based on 6 RCTs.
[5] Not clearly reported in all studies, presumed to be during hospital stay following acute ischemic stroke.
[6] IST is the dominant study in the meta-analysis. In IST allocation was concealed, outcome assessors were blinded; f/u>99%; study not stopped early for benefit; not clear whether analysis was ITT.
[7] 95% CI includes both 1) no effect and 2) appreciable benefit or appreciable harm
[8] Based on meta-analysis by Kamphuisen 2006
[9] Fewer than 300 events occurred.
[10] Statistical heterogeneity: p= 0.003; I squared = 74.3%

Table 3
Summary of Findings: Low molecular weight heparin compared to unfractionated heparin in patients with acute ischemic stroke and restricted mobility

Low molecular weight heparin compared to unfractionated heparin in patients with acute ischemic stroke and restricted mobility

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk		Relative effect (95% CI)	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)
	Risk with Unfractionated heparin	Risk difference with Low molecular weight heparin			
Mortality	**75 deaths per 1000**	**3 fewer per 1000** (from 24 fewer to 17 more)	**RR 0.96** (0.72 to 1.2)[1]	2506 (3 studies) 90 days	⊕⊕⊕◯ **MODERATE**[2] due to imprecision
Pulmonary Embolism	**11 PEs per 1000**[3]	**8 fewer per 1000** (from 1 fewer to 10 fewer)	**RR 0.26** (0.07 to 0.95)	2092 (3 studies) 14 days	⊕⊕⊕◯ **MODERATE**[4] due to imprecision
Symptomatic DVT	**15 DVTs per 1000**[5]	**7 fewer per 1000** (from 3 fewer to 9 fewer)	**RR 0.56** (0.4 to 0.77)	2092 (3 studies) 14 days	⊕⊕⊕◯ **MODERATE**[6] due to imprecision
Symptomatic intra-cranial hemorrhage	**7 bleeding events per 1000**[7]	**2 fewer per 1000** (from 5 fewer to 6 more)	**RR 0.7** (0.26 to 1.83)	1749 (3 studies) 14 days	⊕⊕⊕◯ **MODERATE**[2] due to imprecision
Symptomatic extra-cranial hemorrhage	**5 bleeding events per 1000**[8]	**6 more per 1000** (from 5 fewer to 214 more)	**RR 2.12** (0.09 to 43.78)[9]	2506 (3 studies) 14 days	⊕⊕⊕◯ **MODERATE**[2] due to imprecision

*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] 0.40% mortality due to bleeding in both groups (5/1255 LMWH, 5/1251 UFH)
[2] 95% CI includes both 1) no effect and 2) appreciable benefit or appreciable harm
[3] Baseline risk calculated by multiplying baseline risk in CLOTS study times the RR with any heparin prophylaxis
[4] Fewer than 300 events occurred.
[5] Data for any proximal DVT
[6] Fewer than 300 events occurred.

[7] Based on PREVAIL study data
[8] Based on data from heparin for VTE prevention profile
[9] % due to GI bleeding not reported

Table 4
Summary of Findings: Intermittent pneumatic compression (IPC) compared to No IPC for prevention of VTE in patients with ischemic stroke and restricted mobility

Intermittent pneumatic compression (IPC) compared to No IPC for prevention of VTE in patients with ischemic stroke and restricted mobility

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk		Relative effect (95% CI)	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)
	Risk with No IPC	Risk difference with Intermittent pneumatic compression (IPC)			
Mortality	**87 deaths per 1000**	**22 fewer per 1000** (from 42 fewer to 1 more)	**RR 0.83** (0.68 to 1.01)	3053 (3 studies) 7 - 30 days[1]	⊕⊕⊕◯ **MODERATE**[2] due to imprecision
Symptomatic DVT	**48 DVTs per 1000**	**16 fewer per 1000** (from 1 fewer to 28 fewer)	**RR 0.73** (0.53 to 0.99)[7]	2876 (1 study[3]) 30 days	⊕⊕⊕◯ **MODERATE**[6] due to imprecision
Pulmonary embolism	**16 PEs per 1000**	**4 fewer per 1000** (from 12 fewer to 8 more)[4]	**RR 0.83** (0.51 to 1.35)	2876 (1 study[3]) 30 days	⊕⊕⊕◯ **MODERATE**[5] due to imprecision

*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] CLOTS III trial the outcome was measured at 30 days, in Lacut et al. and Prasad et al. Outcomes were measured at 7 and 10 days, respectively.
[2] CI includes 1
[3] CLOTS III
[4] Baseline risk from the control arm in CLTOS III (2.4%)
[5] Wide CI that include significant benefit and significant harm
[6] only 156 events occurred in both groups
[7] at 6 months follow up the risk of developing sDVT was not statistically significant between both groups RR 0·76 (0·56 to 1·01), we chose to present the 30 days outcome because the intervention was applied for at least 30 days, it is unlikely that the mechanical prophylaxis will have a residual effect at 6 months.

Table 5
Summary of Findings: Elastic compression stockings compared to no elastic compression stockings for patients with ischemic stroke and restricted mobility

Elastic compression stockings compared to no elastic compression stockings for patients with ischemic stroke and restricted mobility

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk		Relative effect (95% CI)	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)
	Risk with No elastic compression stockings	Risk difference with elastic compression stockings			
Mortality	**87 deaths per 1000**[1]	**10 more per 1000** (from 10 fewer to 37 more)	**RR 1.11** (0.88 to 1.42)	2615 (2 studies) 30 days[2]	⊕⊕⊕◯ **MODERATE**[3,4,5] due to imprecision
Pulmonary Embolism	**16 PEs per 1000**[1]	**6 fewer per 1000** (from 11 fewer to 5 more)	**RR 0.65** (0.33 to 1.31)	2518 (1 study[6]) 30 days	⊕⊕⊕◯ **MODERATE**[3,5] due to imprecision
Symptomatic DVT	**48 DVTs per 1000**[1]	**4 fewer per 1000** (from 18 fewer to 14 more)	**RR 0.91** (0.63 to 1.29)[7]	2518 (1 study[6]) 30 days	⊕⊕⊕◯ **MODERATE**[3,5] due to imprecision
Skin complications of elastic compression stockings	**13 skin complications per 1000**[1]	**39 more per 1000** (from 17 more to 77 more)	**RR 4.02** (2.34 to 6.91)	2518 (1 study[6]) 30 days	⊕⊕⊕◯ **MODERATE**[8,9] due to risk of bias

*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] Baseline risks derived from the control arm of CLOTS. Patients included in the trial were judged representative of the population of stroke patients with restricted mobility. Indeed CLOTS used few exclusion criteria (See above)
[2] Follow-up was 30 days in CLOTS and 7±2 days in Muir et al.
[3] Allocation concealed in both studies. Outcome adjudicator blinded in both studies. Intention to treat analysis reported in one study (CLOTS). High rates of follow-up in both studies (100% and 99% for mortality). No study stopped early for benefit.
[4] I2=0%
[5] CI includes both negligible effect and appreciable benefit or appreciable harm
[6] CLOTS trial

[7] CLOTS, the primary study for this analysis found no effect on “Proximal DVT” (adjusted OR 0.98; CI 0.76-1.27)
[8] Assessment of outcomes was based on case-note review and was not blinded to treatment allocation
[9] Although CI excludes no effect, the number of events is low. This along with study limitations warranted rating down of the quality of evidence by one level

Table 6
Summary of Findings: Prophylactic low dose (UFH or LMWH) compared to no prophylaxis in patients with hemorrhagic stroke and restricted mobility

Prophylactic low dose (UFH or LMWH) compared to no prophylaxis in patients with hemorrhagic stroke and restricted mobility

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk		Relative effect (95% CI)	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)
	Risk with No prophylactic low dose heparin	Risk difference with Prophylactic low dose heparin (UFH or LMWH)			
Mortality	**400 deaths per 1000**[1]	**20 more per 1000** (from 216 fewer to 544 more)	**RR 1.05** (0.46 to 2.36)	114 (2 studies[2]) 30 days	⊕⊕◯◯ **LOW**[3,4,5] due to risk of bias, imprecision
Pulmonary Embolism	**16 PEs per 1000**[6]	**5 fewer per 1000** (from 8 fewer to 0 more)	**RR 0.7** (0.47 to 1.03)[7]	10681 (8 studies[7]) 30 days	⊕⊕⊕◯ **MODERATE**[4,5,8,9] due to imprecision
Symptomatic DVT	**48 DVTs per 1000**[6]	**33 fewer per 1000** (from 28 fewer to 38 fewer)	**RR 0.31** (0.21 to 0.42)[7]	914 (8 studies[7]) 30 days	⊕⊕◯◯ **LOW**[4,5,8,9,10] due to inconsistency, imprecision
Rebleeding	**10 rebleeds per 1000**[11]	**8 fewer per 1000** (from 9 fewer to 1 more)	**RR 0.24** (0.05 to 1.13)[12]	189 (3 studies[13]) 10 days[14]	⊕⊕◯◯ **LOW**[4,5,15] due to risk of bias, imprecision

*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] Baseline risk of mortality is derived from: Lancet Neurol. 2010;9(2):167-76
[2] We excluded Orken 2009 from this analysis given the control group received compression stockings which is a confounding factor
[3] Allocation: unclear whether concealed in both studies (Boeer 1991; Dickmann 1988). Unclear whether ITT analysis in both studies. None of the 2 studies stopped early for benefit. None of the studies reported blinding patients.
[4] 95% CI includes both 1) no effect and 2) appreciable benefit or appreciable harm
[5] Fewer than 300 events occurred.
[6] Baseline risks derived from the control arm of CLOTS. Patients included in the trial were judged representative of the population of stroke patients with restricted mobility. Indeed, CLOTS used few exclusion criteria:

patients with peripheral vascular disease, those with diabetic or sensory neuropathy in whom GCS was might cause skin damage; those with subarachnoid haemorrhage

[7] Indirect data from studies of the effects of heparin on DVT and PE in patients with ischemic stroke (See corresponding EP).

[8] IST is the dominant study in the meta-analysis. In IST allocation was concealed, outcome assessors were blinded; f/u>99%; study not stopped early for benefit; not clear whether analysis was ITT.

[9] Although relative risks for PE and DVT are taken form studies of patients with ischemic stroke, we judged that the indirectness is not significant enough to warrant rating down the quality of the evidence.

[10] Statistical heterogeneity: p= 0.003; I squared = 74.3%

[11] Observational data on baseline risk of rebleeding: In one study, of 302 patients with ICH and a control CT 24 hours after admission excluding a progressive haematoma, none experienced major bleeding after being started on LMWH.(Kleindienst, Acta Neurochir (Wien) (2003) 145: 1085–1091). In a second study, of 97 patients with ICH and no clinical evidence of hemorrhage enlargement 36 h after admission, none showed a significant hemorrhage growth after being started on LMWH.(Kiphuth;Cerebrovasc Dis 2009;27:146–150). We use 1% as baseline risk, which is the upper limit of the CI around the incidence derived from these 2 studies.

[12] Indirect evidence from an observational study (Warsay JPMA 58:362;2008): very low incidence in rebleeding with no difference between heparin and no heparin: 1/200 vs. 0/258

[13] Included studies: Orken 2009 (LMWH started >48hrs after hemorrhage; while it compares LMWH to long compression stockings, the effect on rebleeding should be similar to that of a comparison of heparin vs. no heparin); Boeer 1991 (UFH started between day 2 and 4 compared to UFH started on day 10; practical comparison of heparin to no heparin during the follow-up period of interest as outcome was assessed on day 10); and Dickman 1988 (UFH started on day 4 compared to UFH started on day 10; practical comparison of heparin to no heparin during the follow-up period of interest as outcome was assessed on day 10)

[14] We considered the timeframe during which patients are exposed to heparin and at consequently at risk of rebleeding.

[15] Allocation: not concealed in one study (Orken 2009) and unclear whether concealed in 2 studies (Boeer 1991; Dickmann 1988). Unclear whether ITT analysis in the each of the 3 studies. None of the 3 studies stopped early for benefit. In Orken 2009, patients who died prior to day 7 (n=4) were excluded from the study after randomization; however none of them had hematoma enlargement after randomization (author contact). None of the studies reported blinding patients. Only one study (Orken 2009) reported blinding assessors of bleeding outcome.

Table 7
Summary of Findings: Early (day 2) compared to late (day 4) initiation of prophylactic low dose heparin for patients with hemorrhagic stroke and restricted mobility

Early (day 2) compared to late (day 4) initiation of prophylactic low dose heparin for patients with hemorrhagic stroke and restricted mobility

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk: Risk with Late (day 4) initiation of prophylactic low dose heparin	Risk difference with Early (day 2)	Relative effect (95% CI)	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)
Mortality	**400 deaths per 1000**[1,2]	**20 more per 1000** (from 336 fewer to 1000 more)	**RR 1.05** (0.16 to 6.79)	45 (1 study) 30 days	⊕⊕⊖⊖ **LOW**[3,4] due to risk of bias, imprecision
Pulmonary Embolism	**11 PEs per 1000**[2,5]	**7 fewer per 1000** (from 11 fewer to 78 more)	**RR 0.35** (0.01 to 8.11)	45 (1 study) 10 days	⊕⊖⊖⊖ **VERY LOW**[3,4] due to risk of bias, imprecision
Symptomatic DVT	**15 DVTs per 1000**[5]	**5 fewer per 1000** (from 11 fewer to 10 more)	**RR 0.65** (0.25 to 1.69)	45 (1 study) 10 days	⊕⊖⊖⊖ **VERY LOW**[3,4,6] due to risk of bias, indirectness, imprecision
Rebleeding	**10 rebleeding events per 1000**[7]	**7 fewer per 1000** (from 10 fewer to 71 more)	**RR 0.35** (0.01 to 8.11)	45 (1 study) 10 days[8]	⊕⊖⊖⊖ **VERY LOW**[3,4] due to risk of bias, imprecision

*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] Baseline risk of mortality is derived from: Lancet Neurol. 2010;9(2):167-76
[2] The single reported symptomatic PE event was fatal; has been included in both mortality and PE outcome in this evidence profile
[3] Day 2 group not randomly defined. Allocation: unclear whether concealed. Unclear whether ITT analysis used. Study not stopped early for benefit. No reporting of blinding of patients or outcome assessors.
[4] CI includes both negligible effect and appreciable benefit or appreciable harm

[5] Baseline risks derived from the control arm of CLOTS. Patients included in the trial were judged representative of the population of stroke patients with restricted mobility. Indeed, CLOTS used few exclusion criteria: patients with peripheral vascular disease, those with diabetic or sensory neuropathy in whom GCS was might cause skin damage; those with subarachnoid haemorrhage

[6] DVT measured through routine perfusion scintigraphy by day 10. Not reported whether symptomatic and whether proximal vs. distal.

[7] Observational data on baseline risk of rebleeding: In one study, of 302 patients with ICH and a control CT 24 hours after admission excluding a progressive haematoma, none experienced major bleeding after being started on LMWH.(Kleindienst1, Acta Neurochir (Wien) (2003) 145: 1085-1091). In a second study, of 97 patients with ICH and no clinical evidence of hemorrhage enlargement 36 h after admission, none showed a significant hemorrhage growth after being started on LMWH.(Kiphuth;Cerebrovasc Dis 2009;27:146-150) We use 1% as baseline risk, which is the upper limit of the CI around the incidence derived from these 2 studies.

[8] We considered the timeframe during which patients are exposed to heparin and consequently at risk of rebleeding.

Evidence to recommendation framework 1

Guideline Question: Should heparin prophylaxis (UFH or LWMH) be recommended in patients with Hemorrhagic Stroke and restricted mobility when compared to no prophylaxis?

Problem: Adult patients with intracranial haemorrhage and restricted mobility
Option: Prophylactic dose heparin
Comparison: No prophylaxis
Setting: Hospital
Perspective: Individual decision making/policy decision making

Background: Patients with stroke and restricted mobilization are at risk of developing venous thromboembolism (VTE). VTE post stroke is associated with significant morbidity and mortality. There are no studies from the Kingdom of Saudi Arabia (KSA) that describe the prognosis or prevalence of this condition. Dennis et al. conducted an observational study that used duplex ultrasound to screen 5632 patients from the first and second CLOTS trials. Within the first 8 days after a stroke, the prevalence of deep venous thrombosis (DVT) and pulmonary embolism (PE) were 11% and 5%, respectively. Additional 3% developed DVT at 28 days. Furthermore, it is estimated that PE account for 13 to 24% of early deaths after stroke usually occurring in the fourth week but can occur earlier. These studies illustrate the importance of implementing VTE preventive strategies early after a stroke event.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	Is the problem a priority?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐	See table below	Data are from existing litrature, no specific epidemiologic data that target KSA population. The baseline risk of DVT in patients with hemorrhagic stroke may be lower than that in ischemic stroke patients, because of the weak VTE preventive effect of antiplatelet therapy. However, the data on VTE risk in hemorrhagic stroke is of low quality. Hence, we used bseline risk for VTE similar to that of ischemic stroke.

Outcome	Assumed Baseline Risk in Systematic Review	Adult patients with stroke in Saudi Arabia
Mortality	400 per 1000	No data
Pulmonary embolism	16 per 1000	No data
Symptomatic DVT	48 per 1000	No data
Rebleeding	10 per 1000	No data

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
What is the overall certainty of this evidence?	No included studies ☐ | Very low ☐ | Low ☒ | Moderate ☐ | High ☐	***The relative importance or values of the main outcomes of interest:***	No data for patients with ICH, we extrapolated from data on ischemic stroke.
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 ☒	***Summary of the evidence for patients' values and preferences:*** No evidence found	
Are the desirable anticipated effects large?	No ☐ | Probably No ☐ | Uncertain ☐ | Probably Yes ☐ | Yes ☒ | Varies ☐	***Summary of the evidence for the relative effect of interventions***: Please see evidence table and reference list.	Low quality of evidence suggests that prophylactic dose heparin did not increae the risk of death or rebleeding. Moderate and low quality evidence suggested that the use of prophylactic dose heparin reduce the risk of PE and symptomatic DVT (respectively) when compared to no prophylaxis, with no change in the risk of rebleeding.
Are the undesirable anticipated effects small?	No ☒ | Probably No ☐ | Uncertain ☐ | Probably Yes ☐ | Yes ☐ | Varies ☐		

Outcome	Relative importance	Certainty of the evidence
Mortality	Critical	Low
Pulmonary embolism	Critical	Moderate
Symptomatic DVT	Critical	Low
Rebleeding	Critical	Low

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Are the desirable effects large relative to undesirable effects?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐		

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	None	
RESOURCE USE	Is the incremental cost small relative to the net benefits?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	None	We did not identify any cost-effectiveness studies that address this question in the context of Saudi Arabia
EQUITY	What would be the impact on health inequities?	Increased ☐ / Probably increased ☐ / Uncertain ☐ / Probably reduced ☐ / Reduced ☒ / Varies ☐	None	
ACCEPTABILITY	Is the option acceptable to key stakeholders ?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	None	
FEASIBILITY	Is the option feasible to implement?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	None	

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)	KSA MoH panel members **suggest** using prophylactic dose heparin in patients with hemorrhagic stroke and restricted mobility.
Justification	-
Subgroup considerations	No special subgroup consideration
Implementation considerations	No special consideration
Monitoring and evaluation	None
Research priorities	National registry to document the prevalence of VTE in stroke patients

Summary of findings table

Author(s): Alhazzani W
Date: 2013-11-27

Prophylactic low dose (UFH or LMWH) compared to no prophylaxis in patients with hemorrhagic stroke and restricted mobility

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk		Relative effect (95% CI)	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)
	Risk with No prophylactic low dose heparin	Risk difference with Prophylactic low dose heparin (UFH or LMWH)			
Mortality	**400 deaths per 1000**[1]	**20 more per 1000** (from 216 fewer to 544 more)	**RR 1.05** (0.46 to 2.36)	114 (2 studies[2]) 30 days	⨁⨁◯◯ **LOW**[3,4,5] due to risk of bias, imprecision
Pulmonary Embolism	**16 PEs per 1000**[6]	**5 fewer per 1000** (from 8 fewer to 0 more)	**RR 0.7** (0.47 to 1.03)[7]	10681 (8 studies[7]) 30 days	⨁⨁⨁◯ **MODERATE**[4,5,8,9] due to imprecision
Symptomatic DVT	**48 DVTs per 1000**[6]	**33 fewer per 1000** (from 28 fewer to 38 fewer)	**RR 0.31** (0.21 to 0.42)[7]	914 (8 studies[7]) 30 days	⨁⨁◯◯ **LOW**[4,5,8,9,10] due to inconsistency, imprecision
Rebleeding	**10 rebleeds per 1000**[11]	**8 fewer per 1000** (from 9 fewer to 1 more)	**RR 0.24** (0.05 to 1.13)[12]	189 (3 studies[13]) 10 days[14]	⨁⨁◯◯ **LOW**[4,5,15] due to risk of bias, imprecision

*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] Baseline risk of mortality is derived from: Lancet Neurol. 2010;9(2):167-76
[2] We excluded Orken 2009 from this analysis given the control group received compression stockings which is a confounding factor
[3] Allocation: unclear whether concealed in both studies (Boeer 1991; Dickmann 1988). Unclear whether ITT analysis in both studies. None of the 2 studies stopped early for benefit. None of the studies reported blinding patients.

[4] 95% CI includes both 1) no effect and 2) appreciable benefit or appreciable harm
[5] Fewer than 300 events occurred.
[6] Baseline risks derived from the control arm of CLOTS. Patients included in the trial were judged representative of the population of stroke patients with restricted mobility. Indeed, CLOTS used few exclusion criteria: patients with peripheral vascular disease, those with diabetic or sensory neuropathy in whom GCS was might cause skin damage; those with subarachnoid haemorrhage
[7] Indirect data from studies of the effects of heparin on DVT and PE in patients with ischemic stroke (See corresponding EP).
[8] IST is the dominant study in the meta-analysis. In IST allocation was concealed, outcome assessors were blinded; f/u>99%; study not stopped early for benefit; not clear whether analysis was ITT.
[9] Although relative risks for PE and DVT are taken form studies of patients with ischemic stroke, we judged that the indirectness is not significant enough to warrant rating down the quality of the evidence.
[10] Statistical heterogeneity: p= 0.003; I squared = 74.3%
[11] Observational data on baseline risk of rebleeding: In one study, of 302 patients with ICH and a control CT 24 hours after admission excluding a progressive haematoma, none experienced major bleeding after being started on LMWH.(Kleindienst, Acta Neurochir (Wien) (2003) 145: 1085–1091). In a second study, of 97 patients with ICH and no clinical evidence of hemorrhage enlargement 36 h after admission, none showed a significant hemorrhage growth after being started on LMWH.(Kiphuth;Cerebrovasc Dis 2009;27:146–150). We use 1% as baseline risk, which is the upper limit of the CI around the incidence derived from these 2 studies.
[12] Indirect evidence from an observational study (Warsay JPMA 58:362;2008): very low incidence in rebleeding with no difference between heparin and no heparin: 1/200 vs. 0/258
[13] Included studies: Orken 2009 (LMWH started >48hrs after hemorrhage; while it compares LMWH to long compression stockings, the effect on rebleeding should be similar to that of a comparison of heparin vs. no heparin); Boeer 1991 (UFH started between day 2 and 4 compared to UFH started on day 10; practical comparison of heparin to no heparin during the follow-up period of interest as outcome was assessed on day 10); and Dickman 1988 (UFH started on day 4 compared to UFH started on day 10; practical comparison of heparin to no heparin during the follow-up period of interest as outcome was assessed on day 10)
[14] We considered the timeframe during which patients are exposed to heparin and at consequently at risk of rebleeding.
[15] Allocation: not concealed in one study (Orken 2009) and unclear whether concealed in 2 studies (Boeer 1991; Dickmann 1988). Unclear whether ITT analysis in the each of the 3 studies. None of the 3 studies stopped early for benefit. In Orken 2009, patients who died prior to day 7 (n=4) were excluded from the study after randomization; however none of them had hematoma enlargement after randomization (author contact). None of the studies reported blinding patients. Only one study (Orken 2009) reported blinding assessors of bleeding outcome.

SoF References:

1. Boeer A, Voth E, Henze T, Prange HW. Early heparin therapy in patients with spontaneous intracerebral haemorrhage. J Neurol Neurosurg Psychiatry. 1991; 54 (5): 466 - 467.
2. Dickmann U , Voth E , Schicha H , Henze T , Prange H ,Emrich D . Heparin therapy, deep-vein thrombosis and pulmonary embolism after intracerebral hemorrhage. Klin Wochenschr. 1988; 66 (23): 1182 - 1183.

Evidence to recommendation framework 2

Guideline Question: Should prophylactic dose LMWH be used in patient with acute ischemic stroke and restricted mobility, when compared to prophylactic dose UFH?

Problem: Adult patients with acute ischemic stroke and restricted mobility
Option: prophylactic low dose LMWH
Comparison: prophylactic low dose UFH
Setting: Hospital
Perspective: Individual decision making

Background: Patients with stroke and restricted mobilization are at risk of developing venous thromboembolism (VTE). VTE post stroke is associated with significant morbidity and mortality. There are no studies from the Kingdom of Saudi Arabia (KSA) that describe the prognosis or prevalence of this condition. Dennis et al. conducted an observational study that used duplex ultrasound to screen 5632 patients from the first and second CLOTS trials. Within the first 8 days after a stroke, the prevalence of deep venous thrombosis (DVT) and pulmonary embolism (PE) were 11% and 5%, respectively. Additional 3% developed DVT at 28 days. Furthermore, it is estimated that PE account for 13 to 24% of early deaths after stroke usually occurring in the fourth week but can occur earlier. These studies illustrate the importance of implementing VTE preventive strategies early after a stroke event.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	Is the problem a priority?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐	See table below	Data are from existing litrature, no specific epidemiologic data that target KSA population.

Outcome	Assumed Baseline Risk in Systematic Review	Adult patients with stroke in Saudi Arabia
Mortality	75 per 1000	No data
Pulmonary embolism	11 per 1000	No data
Symptomatic DVT	15 per 1000	No data
Symptomatic intracranial hemorrhage	7 per 1000	No data
Symptomatic extracranial hemorrhage	5 per 1000	No data

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
What is the overall certainty of this evidence?	*No included studies* ☐ | *Very low* ☐ | *Low* ☐ | *Moderate* ☒ | *High* ☐	***The relative importance or values of the main outcomes of interest:***	
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:*** No evidence found ***Summary of the evidence for the relative effect of interventions*:** Please see evidence table and reference list.	Moderate quality of evidence suggests that the use of prophylactic dose LMWH reduces the risk of PE and symptomatic DVT when compared to UFH. Moderate quality of evidence suggests that prophylactic dose LMWH does not increae risk of somptomatic intra or extra cranial bleeding when compared to UFH.
Are the undesirable anticipated effects small?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☒ | *Yes* ☐ | ***Varies*** ☐		

Outcome	Relative importance	Certainty of the evidence
Mortality	Critical	Moderate
Pulmonary embolism	Critical	Moderate
Symptomatic DVT	Critical	Moderate
Symptomatic ICH	Critical	Moderate
Symptomatic extra-cranial haemorrhage	Critical	Moderate

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Are the desirable effects large relative to undesirable effects?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ ***Varies*** ☐		

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐	None	
	Is the incremental cost small relative to the net benefits?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐	The average cost per patient due to VTE or bleeding events was lower with enoxaparin versus UFH ($422 vs $662, respectively; net savings $240). The average anticoagulant cost, including drug-administration cost per patient, was lower with UFH versus enoxaparin ($259 vs $360, respectively; net savings $101). When clinical events and drug-acquisition costs were considered, the total hospital cost was lower with enoxaparin versus UFH ($782 vs $922, respectively; savings $140). Hospital cost-savings were greatest ($287) in patients with NIHSS scores14. **Reference**: Pineo G; Lin J; Stern L; et al. Economic Impact of Enoxaparin Versus Unfractionated Heparin for Venous Thromboembolism Prophylaxis in Patients With Acute Ischemic Stroke: A Hospital Perspective of the PREVAIL Trial. Journal of Hospital Medicine 2012; 7:176–182.	We did not identify any cost-effectiveness studies that address this question in the context of Saudi Arabia
EQUITY	What would be the impact on health inequities?	Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☐ Reduced ☒ Varies ☐	None	None
ACCEPTABILITY	Is the option acceptable to key stakeholders ?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐	None	None

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
FEASIBILITY	**Is the option feasible to implement?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐	None	None

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)	KSA MoH panel members **suggest** using prophylactic dose LMWH in patients with acute ischemic stroke and restricted mobility over UFH
Justification	-
Subgroup considerations	None
Implementation considerations	None
Monitoring and evaluation	None
Research priorities	None

Summary of findings table

Author(s): Alhazzani W

Date: 2013-11-27

Low molecular weight heparin compared to unfractionated heparin in patients with acute ischemic stroke and restricted mobility

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk		Relative effect (95% CI)	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)
	Risk with Unfractionated heparin	Risk difference with Low molecular weight heparin			
Mortality	**75 deaths per 1000**	**3 fewer per 1000** (from 24 fewer to 17 more)	**RR 0.96** (0.72 to 1.2)[1]	2506 (3 studies) 90 days	⊕⊕⊕◯ **MODERATE**[2] due to imprecision
Pulmonary Embolism	**11 PEs per 1000**[3]	**8 fewer per 1000** (from 1 fewer to 10 fewer)	**RR 0.26** (0.07 to 0.95)	2092 (3 studies) 14 days	⊕⊕⊕◯ **MODERATE**[4] due to imprecision
Symptomatic DVT	**15 DVTs per 1000**[5]	**7 fewer per 1000** (from 3 fewer to 9 fewer)	**RR 0.56** (0.4 to 0.77)	2092 (3 studies) 14 days	⊕⊕⊕◯ **MODERATE**[6] due to imprecision
Symptomatic intra-cranial hemorrhage	**7 bleeding events per 1000**[7]	**2 fewer per 1000** (from 5 fewer to 6 more)	**RR 0.7** (0.26 to 1.83)	1749 (3 studies) 14 days	⊕⊕⊕◯ **MODERATE**[2] due to imprecision
Symptomatic extra-cranial hemorrhage	**5 bleeding events per 1000**[8]	**6 more per 1000** (from 5 fewer to 214 more)	**RR 2.12** (0.09 to 43.78)[9]	2506 (3 studies) 14 days	⊕⊕⊕◯ **MODERATE**[2] due to imprecision

*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] 0.40% mortality due to bleeding in both groups (5/1255 LMWH, 5/1251 UFH)
[2] 95% CI includes both 1) no effect and 2) appreciable benefit or appreciable harm
[3] Baseline risk calculated by multiplying baseline risk in CLOTS study times the RR with any heparin prophylaxis
[4] Fewer than 300 events occurred.
[5] Data for any proximal DVT

[6] Fewer than 300 events occurred.
[7] Based on PREVAIL study data
[8] Based on data from heparin for VTE prevention profile
[9] % due to GI bleeding not reported

SoF References:

Systematic reviews:

1. Shorr AF, Jackson WL, Sherner JH, Moores LK. Differences between low-molecular-weight and unfractionated heparin for venous thromboembolism prevention following ischemic stroke: a metaanalysis. Chest. 2008 Jan; 133(1):149-55.

Randomized trials:

1. Hillbom, M, Erila, T, Sotaniemi, K, et al Enoxaparin vs heparin for prevention of deep-vein thrombosis in acute ischaemic stroke: a randomized, double-blind study. Acta Neurol Scand2002; 106, 84-92.
2. Diener, HC, Ringelstein, EB, von Kummer, R, et al Prophylaxis of thrombotic and embolic events in acute ischemic stroke with the low-molecular-weight heparin certoparin: results of the PROTECT Trial.Stroke2006; 37,139-144.
3. Sherman, DG, Albers, GW, Bladin, C, et al The efficacy and safety of enoxaparin versus unfractionated heparin for the prevention of venous thromboembolism after acute ischaemic stroke (PREVAIL Study): an open-label randomised comparison.Lancet2007;369,1347-1355.

Evidence to recommendation framework 3

Guideline Question: Should intermittent pneumatic compression (IPC) be used in patients with acute ischemic stroke and restricted mobility, when compared to no IPC?

Problem: Adult patients with acute ischemic stroke and restricted mobility
Option: intermittent pneumatic compression device (IPC)
Comparison: No IPC
Setting: Hospital
Perspective: Individual decision making

Background: Patients with stroke and restricted mobilization are at risk of developing venous thromboembolism (VTE). VTE post stroke is associated with significant morbidity and mortality. There are no studies from the Kingdom of Saudi Arabia (KSA) that describe the prognosis or prevalence of this condition. Dennis et al. conducted an observational study that used duplex ultrasound to screen 5632 patients from the first and second CLOTS trials. Within the first 8 days after a stroke, the prevalence of deep venous thrombosis (DVT) and pulmonary embolism (PE) were 11% and 5%, respectively. Additional 3% developed DVT at 28 days. Furthermore, it is estimated that PE account for 13 to 24% of early deaths after stroke usually occurring in the fourth week but can occur earlier. These studies illustrate the importance of implementing VTE preventive strategies early after a stroke event.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	Is the problem a priority?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐	See table below	Data are from existing litrature, no specific epidemiologic data that target KSA population.

Outcome	Assumed Baseline Risk in Systematic Review	Adult patients with stroke in Saudi Arabia
Mortality	87 per 1000	No data
Pulmonary embolism	16 per 1000	No data
Symptomatic DVT	48 per 1000	No data

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
What is the overall certainty of this evidence?	No included studies ☐ | Very low ☐ | Low ☐ | Moderate ☒ | High ☐	***The relative importance or values of the main outcomes of interest:***	No data for patients with ICH, we extrapolated from data on ischemic stroke.
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 ☒	***Summary of the evidence for patients' values and preferences:*** No evidence found	
Are the desirable anticipated effects large?	No ☐ | Probably No ☐ | Uncertain ☐ | Probably Yes ☒ | Yes ☐ | ***Varies*** ☐	***Summary of the evidence for the relative effect of interventions*:** Please see evidence table and reference list.	Moderate quality of evidence suggests that intermittent pneumatic compression did not change the risk of death when compared to no prophylaxis.However, there was a trend that is not staistically significant. Moderate quality of evidence suggests that the use of IPC reduces the risk of symptomatic DVT (but no PE) when compared to no prophylaxis at 30days. This effect is not observed when patients were assessed at 6 months after randomization.
Are the undesirable anticipated effects small?	No ☐ | Probably No ☐ | Uncertain ☐ | Probably Yes ☒ | Yes ☐ | ***Varies*** ☐		Should be avoided in patients with peripheral vascular disease

Outcome	Relative importance	Certainty of the evidence
Mortality	Critical	Moderate
Pulmonary embolism	Critical	Moderate
Symptomatic DVT	Critical	Moderate

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Are the desirable effects large relative to undesirable effects?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ ***Varies*** ☐		

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	None	None
	Is the incremental cost small relative to the net benefits?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☒ / Yes ☐ / Varies ☐	None	We did not identify any cost-effectiveness studies that address this question in the context of Saudi Arabia
EQUITY	What would be the impact on health inequities?	Increased ☐ / Probably increased ☐ / Uncertain ☐ / Probably reduced ☒ / Reduced ☐ / Varies ☐	None	None
ACCEPTABILITY	Is the option acceptable to key stakeholders ?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	None	None
FEASIBILITY	Is the option feasible to implement?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	None	None

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)	KSA MoH panel **recommends** using intermittent pneumatic compression in patients with acute ischemic stroke and restricted mobility over no prophylaxis
Justification	-
Subgroup considerations	-
Implementation considerations	-
Monitoring and evaluation	-
Research priorities	-

Summary of findings table

Author(s): Alhazzani W
Date: 2013-11-27

Intermittent pneumatic compression (IPC) compared to No IPC for prevention of VTE in patients with ischemic stroke and restricted mobility

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk		Relative effect (95% CI)	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)
	Risk with No IPC	Risk difference with Intermittent pneumatic compression (IPC)			
Mortality	**87 deaths per 1000**	**22 fewer per 1000** (from 42 fewer to 1 more)	**RR 0.83** (0.68 to 1.01)	3053 (3 studies) 7 - 30 days[1]	⨁⨁⨁◯ **MODERATE**[2] due to imprecision
Symptomatic DVT	**48 DVTs per 1000**	**16 fewer per 1000** (from 1 fewer to 28 fewer)	**RR 0.73** (0.53 to 0.99)[7]	2876 (1 study[3]) 30 days	⨁⨁⨁◯ **MODERATE**[6] due to imprecision
Pulmonary embolism	**16 PEs per 1000**	**4 fewer per 1000** (from 12 fewer to 8 more)[4]	**RR 0.83** (0.51 to 1.35)	2876 (1 study[3]) 30 days	⨁⨁⨁◯ **MODERATE**[5] due to imprecision

*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] CLOTS III trial the outcome was measured at 30 days, in Lacut et al. and Prasad et al. Outcomes were measured at 7 and 10 days, respectively.
[2] CI includes 1
[3] CLOTS III
[4] Baseline risk from the control arm in CLTOS III (2.4%)
[5] Wide CI that include significant benefit and significant harm
[6] only 156 events occurred in both groups
[7] at 6 months follow up the risk of developing sDVT was not statistically significant between both groups RR 0·76 (0·56 to 1·01), we chose to present the 30 days outcome because the intervention was applied for at least 30 days, it is unlikely that the mechanical prophylaxis will have a residual effect at 6 months.

SoF References:

Systematic reviews:

1. CLOTS (Clots in Legs Or sTockings after Stroke) Trials Collaboration. Effectiveness of intermittent pneumatic compression in reduction of risk of deep vein thrombosis in patients who have had a stroke (CLOTS 3): a multicentre randomised controlled trial. Lancet 2013, 382: 516–24.

Randomized trials:

1. CLOTS (Clots in Legs Or sTockings after Stroke) Trials Collaboration. Effectiveness of intermittent pneumatic compression in reduction of risk of deep vein thrombosis in patients who have had a stroke (CLOTS 3): a multicentre randomised controlled trial. Lancet 2013, 382: 516–24.

Evidence to recommendation framework 4

Guideline Question: Should Elastic compression stockings be used in patients with acute ischemic stroke and restricted mobility, when compared to no prophylaxis?

Problem: Adult patients with acute ischemic stroke and restricted mobility
Option: Elastic compression stockings
Comparison: No stocking
Setting: Hospital
Perspective: Individual decision making

Background: Patients with stroke and restricted mobilization are at risk of developing venous thromboembolism (VTE). VTE post stroke is associated with significant morbidity and mortality. There are no studies from the Kingdom of Saudi Arabia (KSA) that describe the prognosis or prevalence of this condition. Dennis et al. conducted an observational study that used duplex ultrasound to screen 5632 patients from the first and second CLOTS trials. Within the first 8 days after a stroke, the prevalence of deep venous thrombosis (DVT) and pulmonary embolism (PE) were 11% and 5%, respectively. Additional 3% developed DVT at 28 days. Furthermore, it is estimated that PE account for 13 to 24% of early deaths after stroke usually occurring in the fourth week but can occur earlier. These studies illustrate the importance of implementing VTE preventive strategies early after a stroke event.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	Is the problem a priority?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐	See table below	Data are from existing litrature, no specific epidemiologic data that target KSA population.

Outcome	Assumed Baseline Risk in Systematic Review	Adult patients with stroke in Saudi Arabia
Mortality	87 per 1000	No data
Pulmonary embolism	16 per 1000	No data
Symptomatic DVT	48 per 1000	No data

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
What is the overall certainty of this evidence?	*No included studies* ☐ | *Very low* ☐ | *Low* ☐ | *Moderate* ☒ | *High* ☐	***The relative importance or values of the main outcomes of interest:***	No data for patients with ICH, we extrapolated from data on ischemic stroke.
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*** ☐		Moderate quality of evidence suggests that compression stockings did not significantly change the risk of death, PE or symptomatic DVT when compared to no prophylaxis..
Are the undesirable anticipated effects small?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☒ | *Yes* ☐ | ***Varies*** ☐		
Are the desirable effects large relative to undesirable effects?	*No* ☐ | *Probably No* ☒ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☐ | ***Varies*** ☐		

Outcome	Relative importance	Certainty of the evidence
Mortality	Critical	Moderate
Pulmonary embolism	Critical	Moderate
Symptomatic DVT	Critical	Moderate

Summary of the evidence for patients' values and preferences:

No evidence found

***Summary of the evidence for the relative effect of interventions*:**

Please see evidence table and reference list.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	None	
	Is the incremental cost small relative to the net benefits?	No ☒ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / Varies ☐	None	We did not identify any cost-effectiveness studies that address this question in the context of Saudi Arabia
EQUITY	What would be the impact on health inequities?	Increased ☒ / Probably increased ☐ / Uncertain ☐ / Probably reduced ☐ / Reduced ☐ / Varies ☐	None	
ACCEPTABILITY	Is the option acceptable to key stakeholders ?	No ☒ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / Varies ☐	None	
FEASIBILITY	Is the option feasible to implement?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / Varies ☐	None	Not applicable since the intervention is not effective in improving critical outcomes.

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)	KSA MoH panel **suggests not using** elastic compression stocking in patients with ischemic stroke and restricted mobility for VTE prevention.
Justification	None
Subgroup considerations	None
Implementation considerations	None
Monitoring and evaluation	None
Research priorities	None

Summary of findings table

Author(s): Alhazzani W

Date: 2013-11-27

Elastic compression stockings compared to no elastic compression stockings for patients with ischemic stroke and restricted mobility

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk		Relative effect (95% CI)	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)
	Risk with No elastic compression stockings	Risk difference with elastic compression stockings			
Mortality	**87 deaths per 1000**[1]	**10 more per 1000** (from 10 fewer to 37 more)	**RR 1.11** (0.88 to 1.42)	2615 (2 studies) 30 days[2]	⊕⊕⊕◯ **MODERATE**[3,4,5] due to imprecision
Pulmonary Embolism	**16 PEs per 1000**[1]	**6 fewer per 1000** (from 11 fewer to 5 more)	**RR 0.65** (0.33 to 1.31)	2518 (1 study[6]) 30 days	⊕⊕⊕◯ **MODERATE**[3,5] due to imprecision
Symptomatic DVT	**48 DVTs per 1000**[1]	**4 fewer per 1000** (from 18 fewer to 14 more)	**RR 0.91** (0.63 to 1.29)[7]	2518 (1 study[6]) 30 days	⊕⊕⊕◯ **MODERATE**[3,5] due to imprecision
Skin complications of elastic compression stockings	**13 skin complications per 1000**[1]	**39 more per 1000** (from 17 more to 77 more)	**RR 4.02** (2.34 to 6.91)	2518 (1 study[6]) 30 days	⊕⊕⊕◯ **MODERATE**[8,9] due to risk of bias

*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] Baseline risks derived from the control arm of CLOTS. Patients included in the trial were judged representative of the population of stroke patients with restricted mobility. Indeed CLOTS used few exclusion criteria (See above)
[2] Follow-up was 30 days in CLOTS and 7±2 days in Muir et al.
[3] Allocation concealed in both studies. Outcome adjudicator blinded in both studies. Intention to treat analysis reported in one study (CLOTS). High rates of follow-up in both studies (100% and 99% for mortality). No study stopped early for benefit.
[4] I2=0%
[5] CI includes both negligible effect and appreciable benefit or appreciable harm
[6] CLOTS trial

[7] CLOTS, the primary study for this analysis found no effect on "Proximal DVT" (adjusted OR 0.98; CI 0.76-1.27)
[8] Assessment of outcomes was based on case-note review and was not blinded to treatment allocation
[9] Although CI excludes no effect, the number of events is low. This along with study limitations warranted rating down of the quality of evidence by one level

SoF References:

Randomized trials:

1. CLOTS Trials Collaboration, Dennis M, Sandercock PA, Reid J, Graham C, Murray G, Venables G, Rudd A, Bowler G. Effectiveness of thigh-length graduated compression stockings to reduce the risk of deep vein thrombosis after stroke (CLOTS trial 1): a multicentre, randomised controlled trial. Lancet. 2009 Jun 6;373(9679):1958-65.
2. Muir KW, Watt A, Baxter G, Grosset DG, Lees KR. Randomized trial of graded compression stockings for prevention of deep-vein thrombosis after acute stroke. Q J Med. 2000; 93:359–64.

Evidence to recommendation framework 5

Guideline Question: Should heparin prophylaxis (UFH or LWMH) be recommended in patients with Hemorrhagic Stroke and restricted mobility when compared to no prophylaxis?

Problem: Adult patients with intracranial haemorrhage and restricted mobility
Option: Prophylactic dose heparin
Comparison: No prophylaxis
Setting: Hospital
Perspective: Individual decision making/policy decision making

Background: Patients with stroke and restricted mobilization are at risk of developing venous thromboembolism (VTE). VTE post stroke is associated with significant morbidity and mortality. There are no studies from the Kingdom of Saudi Arabia (KSA) that describe the prognosis or prevalence of this condition. Dennis et al. conducted an observational study that used duplex ultrasound to screen 5632 patients from the first and second CLOTS trials. Within the first 8 days after a stroke, the prevalence of deep venous thrombosis (DVT) and pulmonary embolism (PE) were 11% and 5%, respectively. Additional 3% developed DVT at 28 days. Furthermore, it is estimated that PE account for 13 to 24% of early deaths after stroke usually occurring in the fourth week but can occur earlier. These studies illustrate the importance of implementing VTE preventive strategies early after a stroke event.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	Is the problem a priority?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐	See table below	Data are from existing litrature, no specific epidemiologic data that target KSA population. The baseline risk of DVT in patients with hemorrhagic stroke may be lower than that in ischemic stroke patients, because of the weak VTE preventive effect of antiplatelet therapy. However, the data on VTE risk in hemorrhagic stroke is of low quality. Hence, we used bseline risk for VTE similar to that of ischemic stroke.

Outcome	Assumed Baseline Risk in Systematic Review	Adult patients with stroke in Saudi Arabia
Mortality	400 per 1000	No data
Pulmonary embolism	16 per 1000	No data
Symptomatic DVT	48 per 1000	No data
Rebleeding	10 per 1000	No data

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
What is the overall certainty of this evidence?	*No included studies* ☐ | *Very low* ☐ | *Low* ☒ | *Moderate* ☐ | *High* ☐	***The relative importance or values of the main outcomes of interest:***	No data for patients with ICH, we extrapolated from data on ischemic stroke.
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* ☒	***Summary of the evidence for patients' values and preferences:*** No evidence found	
Are the desirable anticipated effects large?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☒ | ***Varies*** ☐	***Summary of the evidence for the relative effect of interventions*:** Please see evidence table and reference list.	Low quality of evidence suggests that prophylactic dose heparin did not increae the risk of death or rebleeding. Moderate and low quality evidence suggested that the use of prophylactic dose heparin reduces the risk of PE and symptomatic DVT (respectively) when compared to no prophylaxis, with no change in the risk of rebleeding.
Are the undesirable anticipated effects small?	*No* ☒ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☐ | ***Varies*** ☐		

Outcome	Relative importance	Certainty of the evidence
Mortality	Critical	Low
Pulmonary embolism	Critical	Moderate
Symptomatic DVT	Critical	Low
Rebleeding	Critical	Low

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Are the desirable effects large relative to undesirable effects?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ | ***Varies*** ☐		

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	None	
	Is the incremental cost small relative to the net benefits?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	None	We did not identify any cost-effectiveness studies that address this question in the context of Saudi Arabia.
EQUITY	What would be the impact on health inequities?	Increased ☐ / Probably increased ☐ / Uncertain ☐ / Probably reduced ☐ / Reduced ☒ / Varies ☐	None	
ACCEPTABILITY	Is the option acceptable to key stakeholders ?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	None	
FEASIBILITY	Is the option feasible to implement?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	None	

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)	KSA MoH panel members **suggest using** prophylactic dose heparin in patients with hemorrhagic stroke and restricted mobility.
Justification	-
Subgroup considerations	No special subgroup consideration
Implementation considerations	No special consideration
Monitoring and evaluation	None
Research priorities	National registry to document the prevalence of VTE in stroke patients

Summary of findings table

Author(s): Alhazzani W
Date: 2013-11-27

Prophylactic low dose (UFH or LMWH) compared to no prophylaxis in patients with hemorrhagic stroke and restricted mobility

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk		Relative effect (95% CI)	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)
	Risk with No prophylactic low dose heparin	Risk difference with Prophylactic low dose heparin (UFH or LMWH)			
Mortality	**400 deaths per 1000**[1]	**20 more per 1000** (from 216 fewer to 544 more)	**RR 1.05** (0.46 to 2.36)	114 (2 studies[2]) 30 days	⨁⨁◯◯ **LOW**[3,4,5] due to risk of bias, imprecision
PE	**16 PEs per 1000**[6]	**5 fewer per 1000** (from 8 fewer to 0 more)	**RR 0.7** (0.47 to 1.03)[7]	10681 (8 studies[7]) 30 days	⨁⨁⨁◯ **MODERATE**[4,5,8,9] due to imprecision
Symptomatic DVT	**48 DVTs per 1000**[6]	**33 fewer per 1000** (from 28 fewer to 38 fewer)	**RR 0.31** (0.21 to 0.42)[7]	914 (8 studies[7]) 30 days	⨁⨁◯◯ **LOW**[4,5,8,9,10] due to inconsistency, imprecision
Rebleeding	**10 rebleeds per 1000**[11]	**8 fewer per 1000** (from 9 fewer to 1 more)	**RR 0.24** (0.05 to 1.13)[12]	189 (3 studies[13]) 10 days[14]	⨁⨁◯◯ **LOW**[4,5,15] due to risk of bias, imprecision

*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] Baseline risk of mortality is derived from: Lancet Neurol. 2010;9(2):167-76
[2] We excluded Orken 2009 from this analysis given the control group received compression stockings which is a confounding factor
[3] Allocation: unclear whether concealed in both studies (Boeer 1991; Dickmann 1988). Unclear whether ITT analysis in both studies. None of the 2 studies stopped early for benefit. None of the studies reported blinding patients.

[4] 95% CI includes both 1) no effect and 2) appreciable benefit or appreciable harm
[5] Fewer than 300 events occurred.
[6] Baseline risks derived from the control arm of CLOTS. Patients included in the trial were judged representative of the population of stroke patients with restricted mobility. Indeed, CLOTS used few exclusion criteria: patients with peripheral vascular disease, those with diabetic or sensory neuropathy in whom GCS was might cause skin damage; those with subarachnoid haemorrhage
[7] Indirect data from studies of the effects of heparin on DVT and PE in patients with ischemic stroke (See corresponding EP).
[8] IST is the dominant study in the meta-analysis. In IST allocation was concealed, outcome assessors were blinded; f/u>99%; study not stopped early for benefit; not clear whether analysis was ITT.
[9] Although relative risks for PE and DVT are taken form studies of patients with ischemic stroke, we judged that the indirectness is not significant enough to warrant rating down the quality of the evidence.
[10] Statistical heterogeneity: p= 0.003; I squared = 74.3%
[11] Observational data on baseline risk of rebleeding: In one study, of 302 patients with ICH and a control CT 24 hours after admission excluding a progressive haematoma, none experienced major bleeding after being started on LMWH.(Kleindienst, Acta Neurochir (Wien) (2003) 145: 1085–1091). In a second study, of 97 patients with ICH and no clinical evidence of hemorrhage enlargement 36 h after admission, none showed a significant hemorrhage growth after being started on LMWH.(Kiphuth;Cerebrovasc Dis 2009;27:146–150). We use 1% as baseline risk, which is the upper limit of the CI around the incidence derived from these 2 studies.
[12] Indirect evidence from an observational study (Warsay JPMA 58:362;2008): very low incidence in rebleeding with no difference between heparin and no heparin: 1/200 vs. 0/258
[13] Included studies: Orken 2009 (LMWH started >48hrs after hemorrhage; while it compares LMWH to long compression stockings, the effect on rebleeding should be similar to that of a comparison of heparin vs. no heparin); Boeer 1991 (UFH started between day 2 and 4 compared to UFH started on day 10; practical comparison of heparin to no heparin during the follow-up period of interest as outcome was assessed on day 10); and Dickman 1988 (UFH started on day 4 compared to UFH started on day 10; practical comparison of heparin to no heparin during the follow-up period of interest as outcome was assessed on day 10)
[14] We considered the timeframe during which patients are exposed to heparin and at consequently at risk of rebleeding.
[15] Allocation: not concealed in one study (Orken 2009) and unclear whether concealed in 2 studies (Boeer 1991; Dickmann 1988). Unclear whether ITT analysis in the each of the 3 studies. None of the 3 studies stopped early for benefit. In Orken 2009, patients who died prior to day 7 (n=4) were excluded from the study after randomization; however none of them had hematoma enlargement after randomization (author contact). None of the studies reported blinding patients. Only one study (Orken 2009) reported blinding assessors of bleeding outcome.

SoF References:

1. Boeer A, Voth E, Henze T, Prange HW. Early heparin therapy in patients with spontaneous intracerebral haemorrhage. J Neurol Neurosurg Psychiatry. 1991; 54 (5): 466 - 467.
2. Dickmann U , Voth E , Schicha H , Henze T , Prange H ,Emrich D . Heparin therapy, deep-vein thrombosis and pulmonary embolism after intracerebral hemorrhage. Klin Wochenschr. 1988; 66 (23): 1182 - 1183.

Evidence to recommendation framework 6

Guideline Question: Should early (day 2) heparin prophylaxis be recommended in patients with hemorrhagic stroke and restricted mobility when compared to late (day 4) heparin prophylaxis?

Problem: Adult patients with haemorrhagic stroke and restricted mobility
Option: Prophylactic dose heparin started at day 2
Comparison: Prophylactic dose heparin started at day 4
Setting: Hospital
Perspective: Individual decision making/policy decision making

Background: Patients with stroke and restricted mobilization are at risk of developing venous thromboembolism (VTE). VTE post stroke is associated with significant morbidity and mortality. There are no studies from the Kingdom of Saudi Arabia (KSA) that describe the prognosis or prevalence of this condition. Dennis et al. conducted an observational study that used duplex ultrasound to screen 5632 patients from the first and second CLOTS trials. Within the first 8 days after a stroke, the prevalence of deep venous thrombosis (DVT) and pulmonary embolism (PE) were 11% and 5%, respectively. Additional 3% developed DVT at 28 days. Furthermore, it is estimated that PE account for 13 to 24% of early deaths after stroke usually occurring in the fourth week but can occur earlier. These studies illustrate the importance of implementing VTE preventive strategies early after a stroke event.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ *Varies* ☐	See table below	Data are from existing litrature, no specific epidemiologic data that target KSA population.

Outcome	Assumed Baseline Risk in Systematic Review	Adult patients with stroke in Saudi Arabia
Mortality	400 per 1000	No data
Pulmonary embolism	16 per 1000	No data
Symptomatic DVT	48 per 1000	No data
Rebleeding	10 per 1000	No data

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
What is the overall certainty of this evidence?	No included studies ☐ | Very low ☒ | Low ☐ | Moderate ☐ | High ☐	***The relative importance or values of the main outcomes of interest:***	No data for patients with ICH, we extrapolated from data on ischemic stroke.
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:*** No evidence found ***Summary of the evidence for the relative effect of interventions***: Please see evidence table and reference list.	Low quality of evidence from a small RCT that was underpowered to detect mortality difference, the results were imprecise to make conclusions. Very low quality of evidence suggested that the use of early prophylactic dose heparin did not significantly reduce the risk of PE and symptomatic DVT when compared to late heparin use. Very low quality of evidence did not show significant increase in rebleeding rate.
Are the undesirable anticipated effects small?	No ☐ | Probably No ☐ | Uncertain ☒ | Probably Yes ☐ | Yes ☐ | ***Varies*** ☐		

Outcome	Relative importance	Certainty of the evidence
Mortality	Critical	Low
Pulmonary embolism	Critical	Very low
Symptomatic DVT	Critical	Very Low
Rebleeding	Critical	Very Low

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Are the desirable effects large relative to undesirable effects?	No ☐ Probably No ☐ Uncertain ☒ Probably Yes ☐ Yes ☐ Varies ☐		

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐	None	None
	Is the incremental cost small relative to the net benefits?	No ☒ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☐ Varies ☐	None	We did not identify any cost-effectiveness studies that address this question in the context of Saudi Arabia. Cost effectiveness does not apply because of lack of evidence on effectiveness.
EQUITY	What would be the impact on health inequities?	Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☒ Reduced ☐ Varies ☐	None	None
ACCEPTABILITY	Is the option acceptable to key stakeholders ?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐	None	None

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
FEASIBILITY	**Is the option feasible to implement?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ ***Varies*** ☐	None	None

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)	KSA MoH panel members **suggest** starting prophylactic dose heparin in patients with hemorrhagic stroke and restricted mobility between days 2 and 4.
Justification	None
Subgroup considerations	None
Implementation considerations	None
Monitoring and evaluation	None
Research priorities	Larger RCTs are required to further address this question.

Summary of findings table

Author(s): Alhazzani W
Date: 2013-11-27

Early (day 2) compared to late (day 4) initiation of prophylactic low dose heparin for patients with hemorrhagic stroke and restricted mobility

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk		Relative effect (95% CI)	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)
	Risk with Late (day 4) initiation of prophylactic low dose heparin	Risk difference with Early (day 2)			
Mortality	**400 deaths per 1000**[1,2]	**20 more per 1000** (from 336 fewer to 1000 more)	**RR 1.05** (0.16 to 6.79)	45 (1 study) 30 days	⊕⊕⊖⊖ **LOW**[3,4] due to risk of bias, imprecision
Pulmonary Embolism	**11 PEs per 1000**[2,5]	**7 fewer per 1000** (from 11 fewer to 78 more)	**RR 0.35** (0.01 to 8.11)	45 (1 study) 10 days	⊕⊖⊖⊖ **VERY LOW**[3,4] due to risk of bias, imprecision
Symptomatic DVT	**15 DVTs per 1000**[5]	**5 fewer per 1000** (from 11 fewer to 10 more)	**RR 0.65** (0.25 to 1.69)	45 (1 study) 10 days	⊕⊖⊖⊖ **VERY LOW**[3,4,6] due to risk of bias, indirectness, imprecision
Rebleeding	**10 rebleeding events per 1000**[7]	**7 fewer per 1000** (from 10 fewer to 71 more)	**RR 0.35** (0.01 to 8.11)	45 (1 study) 10 days[8]	⊕⊖⊖⊖ **VERY LOW**[3,4] due to risk of bias, imprecision

*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] Baseline risk of mortality is derived from: Lancet Neurol. 2010;9(2):167-76
[2] The single reported symptomatic PE event was fatal; has been included in both mortality and PE outcome in this evidence profile
[3] Day 2 group not randomly defined. Allocation: unclear whether concealed. Unclear whether ITT analysis used. Study not stopped early for benefit. No reporting of blinding of patients or outcome assessors.

[4] CI includes both negligible effect and appreciable benefit or appreciable harm
[5] Baseline risks derived from the control arm of CLOTS. Patients included in the trial were judged representative of the population of stroke patients with restricted mobility. Indeed, CLOTS used few exclusion criteria: patients with peripheral vascular disease, those with diabetic or sensory neuropathy in whom GCS was might cause skin damage; those with subarachnoid haemorrhage
[6] DVT measured through routine perfusion scintigraphy by day 10. Not reported whether symptomatic and whether proximal vs. distal.
[7] Observational data on baseline risk of rebleeding: In one study, of 302 patients with ICH and a control CT 24 hours after admission excluding a progressive haematoma, none experienced major bleeding after being started on LMWH.(Kleindienst1, Acta Neurochir (Wien) (2003) 145: 1085-1091). In a second study, of 97 patients with ICH and no clinical evidence of hemorrhage enlargement 36 h after admission, none showed a significant hemorrhage growth after being started on LMWH.(Kiphuth;Cerebrovasc Dis 2009;27:146-150) We use 1% as baseline risk, which is the upper limit of the CI around the incidence derived from these 2 studies.
[8] We considered the timeframe during which patients are exposed to heparin and consequently at risk of rebleeding.

SoF References:

1. Boeer A, Voth E, Henze T, Prange HW. Early heparin therapy in patients with spontaneous intracerebral haemorrhage. J Neurol Neurosurg Psychiatry. 1991; 54 (5): 466 - 467.

Evidence to recommendation framework 7

Guideline Question: Should prophylactic dose LMWH be used in patients with hemorrhagic stroke and restricted mobility, when compared to prophylactic dose UFH?

Problem: Adult patients with haemorrhagic stroke and restricted mobility
Option: prophylactic low dose LMWH
Comparison: prophylactic low dose UFH
Setting: Hospital
Perspective: Individual decision making/policy decision making

Background: Patients with stroke and restricted mobilization are at risk of developing venous thromboembolism (VTE). VTE post stroke is associated with significant morbidity and mortality. There are no studies from the Kingdom of Saudi Arabia (KSA) that describe the prognosis or prevalence of this condition. Dennis et al. conducted an observational study that used duplex ultrasound to screen 5632 patients from the first and second CLOTS trials. Within the first 8 days after a stroke, the prevalence of deep venous thrombosis (DVT) and pulmonary embolism (PE) were 11% and 5%, respectively. Additional 3% developed DVT at 28 days. Furthermore, it is estimated that PE account for 13 to 24% of early deaths after stroke usually occurring in the fourth week but can occur earlier. These studies illustrate the importance of implementing VTE preventive strategies early after a stroke event.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	Is the problem a priority?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐	See table below	Data are from existing litrature, no specific epidemiologic data that target KSA population.

Outcome	Assumed Baseline Risk in Systematic Review	Adult patients with stroke in Saudi Arabia
Mortality	87 per 1000	No data
Pulmonary embolism	11 per 1000	No data
Symptomatic DVT	15 per 1000	No data
Symptomatic extra-cranial hemorrhage	5 per 1000	No data

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
What is the overall certainty of this evidence?	*No included studies* ☐ | *Very low* ☒ | *Low* ☐ | *Moderate* ☐ | *High* ☐	***The relative importance or values of the main outcomes of interest:***	No data for patients with ICH, we extrapolated from data on ischemic stroke.
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:*** No evidence found ***Summary of the evidence for the relative effect of interventions*:** Please see evidence table and reference list.	This is indirect evidence from ischemic stroke population. We further lowered the quality of evidence for indirecntess. The overall quality of evidence is low. Rebleeding was not addressed in studies comparing LMWH with UFH in hemorrhagic stroke populatiocn, very low quality of evidence suggests that LMWH and UFH does not significanltly iincrease the risk of rebleeding.
Are the undesirable anticipated effects small?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☒ | *Probably Yes* ☐ | *Yes* ☐ | ***Varies*** ☐		

Outcome	Relative importance	Certainty of the evidence
Mortality	Critical	Low
Pulmonary embolism	Critical	Low
Symptomatic DVT	Critical	Low
Symptomatic extra-cranial haemorrhage	Critical	Low
Rebleeding	Critical	Very Low

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Are the desirable effects large relative to undesirable effects?	*No* ☐ *Probably No* ☐ *Uncertain* ☒ *Probably Yes* ☐ *Yes* ☐ ***Varies*** ☐		

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	None	None
	Is the incremental cost small relative to the net benefits?	No ☐ / Probably No ☐ / Uncertain ☒ / Probably Yes ☐ / Yes ☐ / Varies ☐	None	We did not identify any cost-effectiveness studies that address this question in the context of Saudi Arabia.
EQUITY	What would be the impact on health inequities?	Increased ☐ / Probably increased ☐ / Uncertain ☐ / Probably reduced ☒ / Reduced ☐ / Varies ☐	None	None
ACCEPTABILITY	Is the option acceptable to key stakeholders ?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	None	None
FEASIBILITY	Is the option feasible to implement?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	None	None

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)	KSA MoH panel members **suggest using** prophylactic dose LMWH over UFH in patients with hemorrhagic stroke and restricted mobility.
Justification	None
Subgroup considerations	None
Implementation considerations	None
Monitoring and evaluation	None
Research priorities	None

Summary of findings table

Author(s): Alhazzani W
Date: 2013-11-27

Low molecular weight heparin compared to unfractionated heparin in patients with acute ischemic stroke and restricted mobility

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk		Relative effect (95% CI)	No of Participants (studies) Follow-up	Quality of the evidence (GRADE)
	Risk with Unfractionated heparin	Risk difference with Low molecular weight heparin			
Mortality	**87 deaths per 1000**	**3 fewer per 1000** (from 24 fewer to 17 more)	**RR 0.96** (0.72 to 1.2)[1]	2506 (3 studies) 90 days	⊕⊕⊖⊖ **LOW**[2] due to imprecision, indirectness
Pulmonary Embolism	**11 PEs per 1000**[3]	**8 fewer per 1000** (from 1 fewer to 10 fewer)	**RR 0.26** (0.07 to 0.95)	2092 (3 studies) 14 days	⊕⊕⊖⊖ **LOW**[4] due to imprecision, indirectness
Symptomatic DVT	**15 DVTs per 1000**[5]	**7 fewer per 1000** (from 3 fewer to 9 fewer)	**RR 0.56** (0.4 to 0.77)	2092 (3 studies) 14 days	⊕⊕⊖⊖ **LOW**[6] due to imprecision, indirectness
Symptomatic extra-cranial hemorrhage	**5 bleeding events per 1000**[7]	**6 more per 1000** (from 5 fewer to 214 more)	**RR 2.12** (0.09 to 43.78)[8]	2506 (3 studies) 14 days	⊕⊕⊖⊖ **LOW**[2] due to imprecision, indirectness

*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] 0.40% mortality due to bleeding in both groups (5/1255 LMWH, 5/1251 UFH)
[2] 95% CI includes both 1) no effect and 2) appreciable benefit or appreciable harm
[3] Baseline risk calculated by multiplying baseline risk in CLOTS study times the RR with any heparin prophylaxis
[4] Fewer than 300 events occurred.

[5] Data for any proximal DVT
[6] Fewer than 300 events occurred.
[7] Based on data from heparin for VTE prevention profile
[8] % due to GI bleeding not reported
[9] The quality of evidence was lowered for indirectness.

SoF References:

Systematic reviews:

1. Shorr AF, Jackson WL, Sherner JH, Moores LK. Differences between low-molecular-weight and unfractionated heparin for venous thromboembolism prevention following ischemic stroke: a metaanalysis. Chest. 2008 Jan; 133(1):149-55.

Randomized trials:

1. Hillbom, M, Erila, T, Sotaniemi, K, et al Enoxaparin vs heparin for prevention of deep-vein thrombosis in acute ischaemic stroke: a randomized, double-blind study. Acta Neurol Scand2002; 106, 84-92.
2. Diener, HC, Ringelstein, EB, von Kummer, R, et al Prophylaxis of thrombotic and embolic events in acute ischemic stroke with the low-molecular-weight heparin certoparin: results of the PROTECT Trial.Stroke2006; 37,139-144.
3. Sherman, DG, Albers, GW, Bladin, C, et al The efficacy and safety of enoxaparin versus unfractionated heparin for the prevention of venous thromboembolism after acute ischaemic stroke (PREVAIL Study): an open-label randomised comparison.Lancet2007;369,1347-1355.

Evidence to recommendation framework 8

Guideline Question: Should intermittent pneumatic compression (IPC) be used in patients with hemorrhagic stroke and restricted mobility, when compared to no IPC?

Problem: Adult patients with haemorrhagic stroke and restricted mobility
Option: intermittent pneumatic compression device (IPC)
Comparison: No IPC
Setting: Hospital
Perspective: Individual decision making

Background: Patients with stroke and restricted mobilization are at risk of developing venous thromboembolism (VTE). VTE post stroke is associated with significant morbidity and mortality. There are no studies from the Kingdom of Saudi Arabia (KSA) that describe the prognosis or prevalence of this condition. Dennis et al. conducted an observational study that used duplex ultrasound to screen 5632 patients from the first and second CLOTS trials. Within the first 8 days after a stroke, the prevalence of deep venous thrombosis (DVT) and pulmonary embolism (PE) were 11% and 5%, respectively. Additional 3% developed DVT at 28 days. Furthermore, it is estimated that PE account for 13 to 24% of early deaths after stroke usually occurring in the fourth week but can occur earlier. These studies illustrate the importance of implementing VTE preventive strategies early after a stroke event.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	Is the problem a priority?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☒ / Varies ☐	See table below	Data are from existing litrature, no specific epidemiologic data that target KSA population.

Outcome	Assumed Baseline Risk in Systematic Review	Adult patients with stroke in Saudi Arabia
Mortality	400 per 1000	No data
Pulmonary embolism	16 per 1000	No data
Symptomatic DVT	48 per 1000	No data

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
What is the overall certainty of this evidence?	*No included studies* ☐ | *Very low* ☐ | *Low* ☒ | *Moderate* ☐ | *High* ☐	***The relative importance or values of the main outcomes of interest:***	No data for patients with ICH, we extrapolated from data on ischemic stroke.
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* ☒	***Summary of the evidence for patients' values and preferences:*** No evidence found	
Are the desirable anticipated effects large?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☒ | *Yes* ☐ | ***Varies*** ☐	***Summary of the evidence for the relative effect of interventions*:** Please see evidence table and reference list.	This is indirect evidence from ischemic stroke population. Wefurther lowered the quality of evidence for indirectness. The overall quality of evidence is low. The use of IPC reduces the risk of symtomatic DVT but PE. The effect on mortality remains uncertain.
Are the undesirable anticipated effects small?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☒ | ***Varies*** ☐		The main side effect is dyscomfort. Also patients with significant peripheral vascular disease should avoid using IPC. One panelist raised concearns about increased fibrinolytic activity with the use of IPC; we reviewed the litrature and they are contradicting with studies showing increased fibrinolytic activity and studies that did not. However, the risk of rebleeding was not measured in patients receiving IPC. It is not clear if this translate to clinical outcomes.

Outcome	Relative importance	Certainty of the evidence
Mortality	Critical	Moderate
Pulmonary embolism	Critical	Low
Symptomatic DVT	Critical	Low

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Are the desirable effects large relative to undesirable effects?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ ***Varies*** ☐		

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐	None	None
	Is the incremental cost small relative to the net benefits?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐	None	We did not identify any cost-effectiveness studies that address this question in the context of Saudi Arabia.
EQUITY	What would be the impact on health inequities?	Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ☐ Reduced ☒ Varies ☐	None	None
ACCEPTABILITY	Is the option acceptable to key stakeholders ?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐	None	None
FEASIBILITY	Is the option feasible to implement?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☒ Varies ☐	None	None

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)	KSA MoH panel members **suggest** to use intermittent pneumatic compression in patients with ICH and restricted mobility over no prophylaxis
Justification	None
Subgroup considerations	None
Implementation considerations	None
Monitoring and evaluation	None
Research priorities	Studies investigating the effect of IPC in ICH population are required

Summary of findings table

Author(s): Alhazzani W

Date: 2013-11-27

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No IPC	Risk difference with Intermittent pneumatic compression (IPC) (95% CI)
Mortality	3053 (3 studies) 7 - 30 days[1]	⨁⨁⨁◯ **MODERATE**[2] due to imprecision	**RR 0.83** (0.68 to 1.01)	**87 deaths per 1000**	**22 fewer per 1000** (from 42 fewer to 1 more)
Symptomatic DVT	2876 (1 study[3]) 30 days	⨁⨁◯◯ **LOW**[6,8] due to imprecision, indirectness	**RR 0.73** (0.53 to 0.99) [7]	**48 DVTs per 1000**	**16 fewer per 1000** (from 1 fewer to 28 fewer)
Pulmonary embolism	2876 (1 study[3]) 30 days	⨁⨁◯◯ **LOW**[5,8] due to imprecision, indirectness	**RR 0.83** (0.51 to 1.35)	**16 PEs per 1000**	**4 fewer per 1000** (from 12 fewer to 8 more)[4]

*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] CLOTS III trial the outcome was measured at 30 days, in Lacut et al. and Prasad et al. Outcomes were measured at 7 and 10 days, respectively.
[2] CI includes 1
[3] CLOTS III
[4] Baseline risk from the control arm in CLTOS III (2.4%)
[5] Wide CI that include significant benefit and significant harm
[6] only 156 events occurred in both groups
[7] at 6 months follow up the risk of developing sDVT was not statistically significant between both groups RR 0·76 (0·56 to 1·01), we chose to present the 30 days outcome because the intervention was applied for at least 30 days, it is unlikely that the mechanical prophylaxis will have a residual effect at 6 months.
[8] The quality of evidence was lowered for indirectness, this study addressed mainly ischemic stroke population (only 11% had ICH).

SoF References:

Systematic reviews:

1. CLOTS (Clots in Legs Or sTockings after Stroke) Trials Collaboration. Effectiveness of intermittent pneumatic compression in reduction of risk of deep vein thrombosis in patients who have had a stroke (CLOTS 3): a multicentre randomised controlled trial. Lancet 2013, 382: 516–24.

Randomized trials:

2. CLOTS (Clots in Legs Or sTockings after Stroke) Trials Collaboration. Effectiveness of intermittent pneumatic compression in reduction of risk of deep vein thrombosis in patients who have had a stroke (CLOTS 3): a multicentre randomised controlled trial. Lancet 2013, 382: 516–24.


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