ASH Draft Recommendations for Optimal Management of VTE

INTRODUCTION

American Society of Hematology (ASH) guidelines are based on a systematic review of available evidence. Through a structured process, a guideline panel makes judgements about the evidence and forms recommendations.

The public comment period occurs after recommendations are formed but before a manuscript report of the guidelines has been finalized and before ASH organizational approval of the guidelines. Comments collected during the open comment period are provided to the guideline panel for review prior to finalizing the guidelines.

These draft recommendations are not final and therefore are not intended for use or citation.

To submit comments on the draft recommendations, please visit **http://vtemgt.questionpro.com**. Only comments submitted via the online survey will be reviewed by the guideline panel.

The public comment period for these draft recommendations is **December 5, 2017 – January 15, 2018**.

RECOMMENDATIONS

Question 1: In patients receiving oral anticoagulation therapy for VTE treatment, should supplementary patient education be offered vs. no supplementary patient education?

> The ASH guideline panel suggests using supplementary patient education in addition to basic education in patients receiving oral anticoagulation for VTE treatment (conditional recommendation based on very low certainty in the evidence).

Question 2: In patients requiring administration of P-gp inhibitors or inducers and/or strong CYP enzymes inhibitors or inducers should we use an alternative anticoagulant or a DOAC for treatment of VTE?

> The ASH guideline panel suggests using an alternative anticoagulant (such as VKA, LMWH) rather than a DOAC in patients requiring treatment for VTE and administration of P-gp inhibitors or inducers and/or strong CYP enzymes inhibitors or inducers (conditional recommendation based on very low certainty in the evidence).

Question 3: In patients receiving VKA therapy for treatment of VTE should a shorter INR recall interval vs. a longer INR recall interval be used following VKA dose adjustment due to an out of target range INR?

> The ASH guideline panel suggests using an INR recall interval of 4 weeks or shorter rather than intervals longer than 4 weeks following VKA dose adjustment due to an out of target range INR in patients receiving treatment for VTE (conditional recommendation based on very low certainty in the evidence).

Question 4: In patients receiving maintenance VKA therapy for treatment of VTE should a longer (6-12 weeks) INR recall interval vs. a shorter (4-weeks) INR recall interval be used during periods of stable INR control?

> The ASH guideline panel suggests using a longer (6-12 weeks) INR recall interval rather than a shorter (4-weeks) INR recall interval during periods of stable INR control in patients receiving maintenance VKA therapy for treatment of VTE (conditional recommendation based on very low certainty in the evidence).

Question 5: In patients receiving anticoagulation therapy for treatment of VTE should specialized anticoagulation management service care vs. care provided by the patient's physician be used for anticoagulation management?

The ASH guideline panel suggests using specialized anticoagulation management service care rather than care provided by the patient's physician in patients receiving treatment for VTE (conditional recommendation based on very low certainty in the evidence).

Question 6: In patients receiving maintenance VKA therapy for treatment of VTE should point-of-care INR testing by the patient at home (patient self-testing; PST) vs. any other INR testing approach be used?

The ASH guideline panel suggests using home point-of-care INR testing (patient self-testing; PST) over any other INR testing approach except for patient self-management (PSM) in suitable patients (those with demonstrated competency to perform PST and can afford this option) receiving maintenance VKA therapy for treatment of VTE (conditional recommendation based on low certainty in the evidence).

Question 7: In patients receiving maintenance VKA therapy for treatment of VTE should point-of-care INR testing by the patient at home and self-adjustment of VKA dose (patient self-management; PSM) vs. any other management approach be used?

The ASH guideline panel recommends using point-of-care INR testing by the patient at home and self-adjustment of VKA dose (patient self-management; PSM) over any other management approach including patient self-testing in suitable patients (those with demonstrated competency to perform PSM and can afford this option) receiving maintenance VKA therapy for treatment of VTE (strong recommendation based on low certainty in the evidence).

Question 8: Due to renumbering, there is no question #8.

Question 9: In patients with renal dysfunction (creatinine clearance or GFR <30 mL/min) receiving LMWH therapy for treatment of VTE should clinicians monitor anti-factor Xa level to guide LMWH dose adjustment versus no such monitoring?

The ASH guideline panel suggests against using anti-factor Xa level monitoring to guide LMWH dose adjustment in patients with renal dysfunction (creatinine clearance or GFR <30 mL/min) receiving treatment for VTE (conditional recommendation based on very low certainty in the evidence).

Question 10: In patients with obesity receiving LMWH therapy for treatment of VTE should clinicians monitor anti-factor Xa level to guide LMWH dose adjustment versus no such monitoring?

The ASH guideline panel recommends against using anti-factor Xa level monitoring to guide LMWH dose adjustment in patients with obesity receiving for treatment of VTE (strong recommendation based on very low certainty in the evidence).

Question 11: In patients with creatinine clearance ≥50 mL/min receiving DOAC therapy for treatment of VTE should renal function be monitored every 6-12 months vs. no such monitoring?

In patients with creatinine clearance ≥50 mL/min receiving DOAC therapy for treatment of VTE, the ASH guideline panel believes that good practice includes renal function monitoring every 6-12 months (ungraded good practice statement).

Question 12: Due to renumbering, there is no question #12.

Question 13: In patients receiving treatment for VTE who survive an episode of anticoagulation therapy related major bleeding should resumption of oral anticoagulation therapy vs. discontinuation of oral anticoagulation therapy be used?

The ASH guideline panel suggests resumption of oral anticoagulation therapy within 90 days rather than discontinuation of oral anticoagulation therapy in patients receiving treatment for VTE who survive an episode of oral anticoagulation therapy related major bleeding and who are at moderate to high risk for recurrent VTE and not at high risk for recurrent bleeding (conditional recommendation based on very low certainty in the evidence).

Question 14: In patients receiving VKA for treatment of VTE with INR >4.5 but <10 and without clinically relevant bleeding should temporary cessation of VKA plus administration of vitamin K vs. temporary cessation of VKA alone be used?

The ASH guideline panel suggests not using vitamin K in addition to temporary cessation of VKA in patients receiving VKA for treatment of VTE with INR >4.5 but <10 and without clinically relevant bleeding (conditional recommendation based on very low certainty in the evidence).

Question 15: In patients with VKA-related life-threatening bleeding during treatment for VTE should 4-factor prothrombin complex concentrates (PCC) vs. fresh-frozen plasma (FFP) be used, in addition to temporary cessation of VKA and intravenous vitamin K?

The ASH guideline panel suggests using 4-factor PCC rather than FFP, in addition to temporary cessation of VKA and intravenous vitamin K in patients with VKA-related life-threatening bleeding during treatment for VTE (conditional recommendation based on very low certainty in the evidence).

Question 16: In patients with dabigatran related life-threatening bleeding during treatment for VTE should temporary cessation of dabigatran plus idarucizumab administration vs. temporary cessation of dabigatran alone be used?

The ASH guideline panel suggests using idarucizumab in addition to temporary cessation of dabigatran rather than no idarucizumab in patients with dabigatran related life-threatening bleeding during treatment for VTE (conditional recommendation based on very low certainty in the evidence).

Question 17a: In patients with oral direct Xa inhibitor related life-threatening bleeding during treatment for VTE should temporary cessation of oral direct Xa inhibitor plus 4-factor prothrombin complex concentrates (PCC) administration vs. temporary cessation of oral direct Xa inhibitor alone be used?

The ASH guideline panel suggests not using 4-factor PCC administration in addition to temporary cessation of oral direct Xa inhibitor in patients with life-threatening bleeding during treatment for VTE (conditional recommendation based on very low certainty in the evidence).

Question 17b: In patients with oral direct Xa inhibitor related life-threatening bleeding during treatment for VTE should temporary cessation of oral direct Xa inhibitor plus andexanet vs. temporary cessation of oral direct Xa inhibitor alone be used?

The ASH guideline panel suggests using andexanet in addition to temporary cessation of oral direct Xa inhibitor rather than no andexanet in patients with direct Xa inhibitor related life-threatening bleeding during treatment for VTE (conditional recommendation based on very low certainty in the evidence).

Question 18: In patients with LMWH or UFH related life-threatening bleeding during treatment for VTE should temporary cessation of LMWH or UFH plus protamine vs. temporary cessation of LMWH or UFH alone be used?

The ASH guideline panel suggests using protamine in addition to temporary cessation of LMWH or UFH rather than no protamine in patients with LMWH or UFH related life-threatening bleeding during treatment for VTE (conditional recommendation based on very low certainty in the evidence).

Question 19a: In patients receiving anticoagulation therapy for treatment of VTE should a daily lottery to improve medication adherence vs. no daily lottery be used?

The ASH guideline panel suggests not using a daily lottery to improve medication adherence in patients receiving anticoagulation therapy for treatment of VTE (conditional recommendation based on very low certainty in the evidence).

Question 19b: In patients receiving anticoagulation therapy for treatment of VTE should electronic reminders to improve medication adherence vs. no electronic reminders be used?

The ASH guideline panel suggests not using electronic reminders to improve medication adherence in patients receiving anticoagulation therapy for treatment of VTE (conditional recommendation based on very low certainty in the evidence).

Question 19c: In patients receiving anticoagulation therapy for treatment of VTE should a daily lottery plus electronic reminders to improve medication adherence vs. no daily lottery or electronic reminders be used?

The ASH guideline panel recommends not using a daily lottery plus electronic reminders to improve medication adherence in patients receiving anticoagulation therapy for treatment of VTE (strong recommendation based on very low certainty in the evidence).

Question 19d: In patients receiving anticoagulation therapy for treatment of VTE should a visual medication schedule to improve medication adherence vs. no visual medication schedule be used?

The ASH guideline panel suggests not using visual medication schedules to improve medication adherence in patients receiving anticoagulation therapy for treatment of VTE (conditional recommendation based on very low certainty in the evidence).

Question 20: In patients receiving DOAC therapy for the treatment of VTE should measurement of the DOAC anticoagulant effect vs. no measurement of the DOAC anticoagulant effect be used during management of DOAC-related bleeding?

The ASH guideline panel suggests not measuring the DOAC anticoagulant effect during management of DOAC-related bleeding in patients receiving treatment for VTE (conditional recommendation based on very low certainty in the evidence).

Question 21: In patients with creatinine clearance <50 mL/min receiving DOAC therapy for treatment of VTE should renal function be monitored more frequently (every 3 months) vs. no such monitoring?

In patients with creatinine clearance <50 mL/min receiving DOAC therapy for treatment of VTE, the ASH guideline panel believes good practice includes renal function monitoring approximately every 3 months (ungraded good practice statement).

Question 22: In obese patients receiving LMWH therapy for treatment of acute VTE should initial LMWH dose selection according to actual body weight vs. capped LMWH doses be used?

The ASH guideline panel suggests initial LMWH dose selection according to actual body weight rather than dose selection based on capped doses in obese patients receiving treatment for acute VTE (conditional recommendation based on very low certainty in the evidence).

Question 23: In patients at low to moderate risk of recurrent VTE who require interruption of VKA therapy for invasive procedures should peri-procedural bridging with LMWH or UHF vs. interruption of VKA therapy alone be used?

The ASH guideline panel recommends against peri-procedural bridging with LMWH or UHF during interruption of VKA therapy in patients at low to moderate risk of recurrent VTE who require invasive procedures (strong recommendation based on low certainty in the evidence).

Question 24: In patients interrupting DOAC therapy for invasive procedures should confirmation of absence of DOAC anticoagulant effect be used vs. interrupting DOAC therapy alone?

The ASH guideline panel suggests not confirming the absence of DOAC anticoagulant effect prior to procedures in patients interrupting DOAC therapy for invasive procedures (conditional recommendation based on very low certainty in the evidence).

Question 25: In patients transitioning from DOAC to VKA should LMWH or UFH bridge therapy vs. overlapping DOAC therapy be used until the INR is within the therapeutic range?

The ASH guideline panel suggests not using LMWH or UFH bridge therapy in favor of overlapping DOAC therapy in patients on DOAC for VTE treatment and transitioning from DOAC to VKA until the INR is within the therapeutic range (conditional recommendation based on very low certainty in the evidence)

Question #1

Should **supplementary patient education** vs. **basic education alone** be used in **patients receiving oral anticoagulation therapy for VTE treatment**?

POPULATION:	patients receiving oral anticoagulation therapy for VTE treatment	**BACKGROUND:**	Greater patient knowledge about oral anticoagulation treatment has been associated with better overall anticoagulation control which may be predictive of better outcomes.[1] However assessments of patient knowledge pertaining to anticoagulation have revealed suboptimal levels of understanding, and patients often overestimate non-severe anticoagulation-related situations and underestimate severe situations due to failure to recognize adverse event symptoms.[2-6] A systematic review of RCTs conducted to evaluate the impact of supplemental patient education, i.e. over and above what most patients routinely receive from healthcare providers, concluded that there was a lack of evidence to support supplemental patient education as a mechanism to improve outcomes in patients with VTE.[7] The quality of evidence reviewed was deemed to have a high risk of bias but newer high quality studies might provide more information.
INTERVENTION:	supplementary patient education		
COMPARISON:	no supplementary patient education		
MAIN OUTCOMES:	Mortality; Pulmonary Embolism - Moderate; Deep Venous Thrombosis in the Upper Leg - Moderate; Bleeding Events; Time in Therapeutic INR Range; Knowledge Scores;		
SETTING:	Inpatient or Outpatient		
PERSPECTIVE:	Clinical recommendation – Population perspective		

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies	Greater patient knowledge about oral anticoagulation treatment has been associated with better overall anticoagulation control which may be predictive of better outcomes.[1] However assessments of patient knowledge pertaining to anticoagulation have revealed suboptimal levels of understanding, and patients often overestimate non-severe anticoagulation-related situations and underestimate severe situations due to failure to recognize adverse event symptoms.[2-6]	

	○ Don't know	A systematic review of RCTs conducted to evaluate the impact of supplemental patient education, i.e. over and above what most patients routinely receive from healthcare providers, concluded that there was a lack of evidence to support supplemental patient education as a mechanism to improve outcomes in patients with VTE.[7] The quality of evidence reviewed was deemed to have a high risk of bias but newer high quality studies might provide more information.	
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	For research evidence on Desirable and Undesirable anticipated effects, as well as the certainty of this evidence, see the **Evidence Profile** in the **Appendix**.	Desirable effects included a reduction in Mortality and VTE, and an increase in TTR. Patients in the supplemental education group may have more easily recognized signs and symptoms of thrombosis prompting them to seek care. All panel members agreed with small but it was remarked that some panel members may have called this effect trivial.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		All effects were in the direction of a reduction in harm, which includes bleeding. A concern was raised that better educated patients may have a greater risk of bleeding because they adhere better to the prescribed oral anticoagulation.

			There was no impact on health-related quality of life. Other potential downsides of providing education were not measured.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies		Major Bleeding had Very Low certainty due to high risk of bias, serious indirectness and serious imprecision. All other outcomes had Low certainty.
VALUES	**Is there important uncertainty about or variability in 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	**Utility related information - the relative importance of outcomes** *Relative importance of the outcomes on a scale 0.00-1.00 with 1.00 indicating a patient comparing the outcome with being in 'Full health' and 0.00 comparing the outcome with being 'Dead'* Our systematic review found that the relative importance of the outcomes is as follows: - Pulmonary embolism: 0.63-0.93 (different methods)[8-10] - Deep vein thrombosis: 0.64-0.99 (different methods)[8-12] - Deep vein thrombosis patients' own current health: 0.95 (Time trade off)[10] - Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off)[8, 10] - Muscular bleeding: 0.76 (time trade off)[10]	Patient representatives' comments: Knowing that bleeding is reversible provides some comfort. All outcomes are important. However, some patients may weigh some outcomes more than others. Patients will have different ways of, and desire for, seeking information. One abstention, otherwise agreement with possibly important uncertainty or variability. For patients taking VKA, time outside of therapeutic range potentially adds burden and anxiety to patients.

		- Minor intracranial bleeding event: 0.75 (standard gamble)[8] - Major intracranial bleeding event: 0.15 (standard gamble)[8] - Central nervous system bleeding: 0.29-0.60 (standard gamble)[13, 14] Our survey among ASH guideline panel members found that the relative importance of QoL and TTR is as follows: - Quality of life (QoL) impairment: 0.57 [SD 0.23] (ASH panels utility rating) - Low time in therapeutic range (TTR): 0.74 [SD 0.25] (ASH panels utility rating)	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		Very low quality evidence showed small desirable effects and trivial undesirable effects, with possibly important uncertainty or variability in how much people value the outcomes. Interpretation of probably includes in some instances "possibly". Panel members remarked that the evidence is less extensive than anticipated and the benefits were, in view of the Very low certainty, not suggestive of a large effect.

RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know	**The following economic analyses were identified:** <u>Resource use for patient education</u> Time requirement of educational sessions known for two included RCTs: 5 minutes video[15]; 20-30 minutes one-on-one teaching session[16] <u>Cost of clinical events</u> Cost of PE (event cost): $11,616 [17] Cost of recurrent VTE (outpatient, hospitalization, and pharmacy cost in 1-year following VTE event): $11,120 [18] Cost of bleeding:[18] - 6 months following DVT: $11,018 for patients with major bleed - Per-event cost estimated over variable follow-up (mean follow-up = 21.3 months): $22,885 for bleed event requiring hospitalization - Per-event cost: base case treatment of bleeds = $9,935	Intervention variably defined in the included studies. The panel felt that the uncertainty about the resource requirements is largely depending on the type of intervention.
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies		Evidence from few studies with Very low quality.

COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	The panel decided that no judgement could be provided as no cost-effectiveness studies were identified, and the evidence for Desirable and Undesirable anticipated effects as well as for Resource Use was of Very Low quality.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified.	The panel judged that the following considerations will increase health equity when the intervention is implemented: Individual patients will have different experiences when the supplemental education is delivered. This also applies to the health care providers who may deliver the intervention differentially. There may be differences between patients receiving DOACs compared with VKA given that patients on DOAC may not be cared for in anticoagulation clinics. Some panel members felt that given the current state of education, supplemental education might increase equity if it is applied to patients who are currently disadvantaged. This might provide impetus to

			reconsider funding decisions for anticoagulation clinics. If the interventions are uniformly administered in a consistent way then health equity would probably be increased. One panel member voted for "Don't know".
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Observational evidence showed the following facilitators:** <u>Patients</u> Patients are typically accepting of anticoagulation education, especially when delivered by their physician and using printed materials or videos.[15, 19, 20]	The following reasons were considered by the panel: Patients: the identified evidence indicates that education is acceptable for patients. Health care providers: likely to find patient education acceptable. Payers: their support may vary in different health systems due to the lack of a clear net benefit of patient education.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified.	Depending on the type of supplemental material, the intervention is less feasible for patients with a lower educational level or patients whose mother tongue differs from that of the educational material.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know	
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies	

	JUDGEMENT							IMPLICATIONS
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**	
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Should supplementary patient education vs. basic education alone be used in patients receiving oral anticoagulation therapy for VTE treatment?

Type of recommendation

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○

Conclusions

RECOMMENDATION	The ASH guideline panel suggests using supplementary patient education in addition to basic education in patients receiving oral anticoagulation for VTE treatment (conditional recommendation based on very low certainty in the evidence).
JUSTIFICATION	One panel member felt that the middle option (either the intervention or the comparator) was appropriate. The guideline panel determined that there is a very low certainty of evidence for a net health benefit from using supplemental educational interventions. Based on the body of available evidence, it is possible that supplemental education reduces mortality and the risk of developing recurrent VTE and possibly also the development of bleeding. There is low certainty that there is an effect of supplemental education on TTR for patients receiving VKA therapy. Not surprisingly, supplemental education increased performance on knowledge assessments; however, this outcome was not prioritized as important by guideline panel members and is of questionable clinical relevance.
SUBGROUP CONSIDERATIONS	No subgroup considerations.
IMPLEMENTATION CONSIDERATIONS	The panel considered the interventions delivered in the trials focusing on face-to-face or ear-to-ear time.

MONITORING AND EVALUATION	No recommendation on monitoring and evaluation.
RESEARCH PRIORITIES	The panel identified the following additional research priorities: 1) A standardized definition of what constitutes a patient education intervention would be helpful 2) More information regarding DOAC educational interventions is needed

References for Evidence to Decision (EtD) table

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Appendix – Evidence Profile

Q1. In patients receiving oral anticoagulation therapy for VTE treatment, should supplementary patient education be offered vs. no supplementary patient education?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**supplementary patient education in addition to basic education received by most patients**	**basic education alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality (follow up: mean 12 months)												
1 [1]	randomised trials	not serious	not serious [a]	not serious	very serious [b]	none	0/46 (0.0%)	3.9% [c]	RR 0.37 (0.02 to 8.83)	**25 fewer per 1,000** (from 38 fewer to 305 more)	⊕⊕◯◯ LOW	CRITICAL
								3.9% [c]		**25 fewer per 1,000** (from 38 fewer to 305 more)		
Pulmonary Embolism - Moderate (follow up: range 3 months to 12 months; assessed with: Thromboembolic events)												
4 [1-4]	randomised trials	serious [d]	not serious	not serious	serious [b]	none	4/268 (1.5%) [f]	1.9% [c,e]	RR 0.57 (0.17 to 1.95)	**8 fewer per 1,000** (from 16 fewer to 18 more)	⊕⊕◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**supplementary patient education in addition to basic education received by most patients**	**basic education alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
								2.0% [c,e]		**9 fewer per 1,000** (from 17 fewer to 19 more)		
Deep Venous Thrombosis in the Upper Leg - Moderate (follow up: range 3 months to 12 months; assessed with: Thromboembolic events)												
4 [1-4]	randomised trials	serious [d]	not serious	not serious	serious [b]	none	4/268 (1.5%) [f]	2.1% [c,e]	RR 0.57 (0.17 to 1.95)	**9 fewer per 1,000** (from 17 fewer to 20 more)	⊕⊕◯◯ LOW	CRITICAL
								2.6% [c,e]		**11 fewer per 1,000** (from 22 fewer to 25 more)		
Bleeding Events (follow up: range 3 months to 12 months)												
4 [1-4]	randomised trials	serious [d]	serious [f]	not serious	serious [b]	none	4/265 (1.5%) [f]	1.1% [c,e,g]	RR 0.54 (0.06 to 4.76)	**5 fewer per 1,000** (from 10 fewer to 41 more)	⊕◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**supplementary patient education in addition to basic education received by most patients**	**basic education alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
								1.7% [c,e,g]		**8 fewer per 1,000** (from 16 fewer to 64 more)		
								2.1% [c,e,g]		**10 fewer per 1,000** (from 20 fewer to 79 more)		
Time in Therapeutic INR Range (follow up: range 3 months to 12 months; Scale from: 0 to 100)												
4 [1-3, 5]	randomised trials	serious [d]	not serious	not serious	serious [b]	none	196 [h]	303 [h]	-	MD **2.4 % higher** (2.79 lower to 7.58 higher)	⊕⊕◯◯ LOW	IMPORTANT
Knowledge Scores (follow up: range 1 days to 6 months)												
5 [4-8]	randomised trials	very serious [d,i]	not serious	not serious	not serious	none	282 [j]	299 [j]	-	SMD **0.77 SD higher** (0.43 higher to 1.11 higher)	⊕⊕◯◯ LOW	NOT IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **SMD:** Standardised mean difference

Explanations

a. Inconsistency cannot be determined as only one RCT reported mortality[1]

b. Lower and upper bounds of the 95% CI for the anticipated absolute effect include important benefit and important harm

c. Median annual risk among 11 RCTs comparing LMWH/VKA with DOAC in patients requiring treatment for VTE.[9-19] This risk was observed in the original trial at 6 months and to obtain the annual risk, we assumed a linear increase over time and doubled the risk observed at 6 months. See also the ASH guideline on Treatment of VTE

d. All RCTs had high RoB, primarily due to lack of blinding of participants, providers and outcome assessors, as well as lack of details on random sequence generation and allocation concealment.

e. Results are adjusted for the design effect of one cluster RCT (Pernod 2008)[4]

f. Unexplained inconsistency with widely different point estimates and I^2=65%

g. High bleeding risk of 2.1% in patients treated with anticoagulants for 6 months, from a systematic review of 13 prospective cohort studies and 56 randomized trials.[20] See also the ASH guideline on Treatment of VTE

h. Results adjusted for design effect of one cluster RCT (Vormfelde 2014)[5]

i. In addition to the RoB issues as noted for the other outcomes, the outcome of knowledge was measured using non-validated questionnaires

j. Results adjusted for design effect of cluster RCTs (Pernod 2008, Vormfelde 2014)[4, 5]

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Question#2

Should **an alternative anticoagulant** vs. **DOAC** be used for **patients requiring administration of P-gp inhibitors or inducers and/or strong CYP enzymes inhibitors or inducers**?

POPULATION:	patients requiring administration of P-gp inhibitors or inducers and/or strong CYP enzymes inhibitors or inducers
INTERVENTION:	an alternative anticoagulant
COMPARISON:	DOAC
MAIN OUTCOMES:	Mortality; PE - Moderate Severity; DVT in the Upper Leg - Moderate Severity; Major Bleeding; Quality of Life Impairment;
SETTING:	Initiation of therapy
PERSPECTIVE:	Clinical recommendation – Population perspective

BACKGROUND: DOAC absorption is mediated by P-gp proteins and therefore P-gp inhibitors/inducers potentially modify the absorption and effect of DOAC. Further, CYP enzymes are involved in the metabolism of oral direct Xa inhibitors and strong inhibitors/inducers of CYP enzymes potentially modify the metabolism and effect of these DOACs. It is uncertain whether patients who require such potentially interacting drugs for DOACs would have better outcomes if instead of a DOAC they would receive another anticoagulant (vitamin K antagonist).

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	DOAC absorption is mediated by P-gp proteins and therefore P-gp inhibitors/inducers potentially modify the absorption and effect of DOAC. Further, CYP enzymes are involved in the metabolism of oral direct Xa inhibitors and strong inhibitors/inducers of CYP enzymes potentially modify the metabolism and effect of these DOACs. It is uncertain whether patients who require such potentially interacting drugs for DOACs would have better outcomes if instead of a DOAC they would receive an alternative anticoagulant (vitamin K antagonist).	

DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	For research evidence on Desirable and Undesirable anticipated effects, as well as the certainty of this evidence, see the **Evidence Profile** in the **Appendix**.	
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know		
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ○ Low ○ Moderate ○ High ● No included studies		
VALUES	**Is there important uncertainty about or variability in 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	**Utility related information - the relative importance of outcomes** *Relative importance of the outcomes on a scale 0.00-1.00 with 1.00 indicating a patient comparing the outcome with being in 'Full health' and 0.00 comparing the outcome with being 'Dead'* Our systematic review found that the relative importance of the outcomes is as follows:	

		- Pulmonary embolism: 0.63-0.93 (different methods)[1-3] - Deep vein thrombosis: 0.64-0.99 (different methods)[1-5] - Deep vein thrombosis patients' own current health: 0.95 (Time trade off)[3] - Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off)[1, 3] - Muscular bleeding: 0.76 (time trade off)[3] - Minor intracranial bleeding event: 0.75 (standard gamble)[3] - Major intracranial bleeding event: 0.15 (standard gamble)[1] - Central nervous system bleeding: 0.29-0.60 (standard gamble)[6, 7] Our survey among ASH guideline panel members found that the relative importance of QoL is as follows: - Quality of life (QoL) impairment: 0.57 [SD 0.23] (ASH panels utility rating)	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know		The lack of evidence for effects on important outcomes precluded the panel to judge the balance of effects.

RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know	**The following economic analyses were identified:** <u>Cost of clinical events</u> Cost of PE (event cost): $11,616 [8] Cost of recurrent VTE (outpatient, hospitalization, and pharmacy cost in 1-year following VTE event): $11,120 [9] Cost of bleeding:[9] - 6 months following DVT: $11,018 for patients with major bleed - Per-event cost estimated over variable follow-up (mean follow-up = 21.3 months): $22,885 for bleed event requiring hospitalization - Per-event cost: base case treatment of bleeds = $9,935 <u>Cost of medications</u>[10] - Warfarin, per month: $15.84 - $51.50 - DOAC, per month: $300.42 - $600.88 - UFH, per week: $37.00 - LMWH, per week: $199.92 - $712.00	Moderate savings: assumption is that VKA (including monitoring) will be less expensive than DOAC. Few patients would be expected to receive LMWH.

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies		
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No evidence on cost-effectiveness identified.	
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know	No research evidence identified.	The direction or impact on health equity is uncertain, as DOAC can have higher out-of-pocket costs, but LMWH/VKA has potential for higher bleeding risk.

ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	No research evidence identified.	The following reasons were considered by the panel: Unknown potential for increased risk for bleeding or VTE, depending on whether the drug is an inducer or inhibitor. Acceptability also depends on the preference to give priority to avoiding bleeding or VTE.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified.	Requirement for anticoagulation monitoring may be a barrier for some patients who cannot or do not want to perform anticoagulation monitoring.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**	
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**	
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			**No included studies**	

	JUDGEMENT							IMPLICATIONS
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**	
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Conclusions

Should an alternative anticoagulant vs. DOAC be used for patients requiring administration of P-gp inhibitors or inducers and/or strong CYP enzymes inhibitors or inducers?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ●	Strong recommendation for the intervention ○
RECOMMENDATION	The ASH guideline panel suggests using an alternative anticoagulant (such as VKA, LMWH) rather than a DOAC in patients requiring treatment for VTE and administration of P-gp inhibitors or inducers and/or strong CYP enzymes inhibitors or inducers (conditional recommendation based on very low certainty in the evidence).				
JUSTIFICATION	This suggestion is mainly based on the ability to monitor the anticoagulant response (VKA) or lack of interaction potential (LMWH). Patient values and preferences should be taken into consideration. Those who are adverse to INR monitoring or daily injections are likely to choose DOACs.				
SUBGROUP CONSIDERATIONS	No subgroup considerations.				
IMPLEMENTATION CONSIDERATIONS	No implementation considerations.				
MONITORING AND EVALUATION	No monitoring and evaluation considerations.				
RESEARCH PRIORITIES	The panel identified the following additional research question: What are the real-world clinical outcomes associated with concomitant administration of DOACs with strong P-gp/CYP3A4 inhibitors/inducers?				

References for Evidence to Decision (EtD) table

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Appendix - Evidence Profile

Q2. In patients requiring administration of P-gp inhibitors or inducers and/or strong CYP enzymes inhibitors or inducers should we use an alternative anticoagulant or a DOAC for treatment of VTE?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	an alternative anticoagulant (such as VKA, LMWH)	DOAC	Relative (95% CI)	Absolute (95% CI)		
Mortality - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
PE - Moderate Severity - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
DVT in the Upper Leg - Moderate Severity - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Major Bleeding - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Quality of Life Impairment - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

CI: Confidence interval

Question #3

Should **a shorter INR recall interval** vs. **a longer INR recall interval** be used **following VKA dose adjustment due to an out of target range INR** in **patients receiving VKA therapy for treatment of VTE**?

POPULATION:	patients receiving VKA therapy for treatment of VTE
INTERVENTION:	a shorter INR recall interval following VKA dose adjustment due to an out of target range INR
COMPARISON:	a longer INR recall interval
MAIN OUTCOMES:	Mortality; PE - Moderate severity; DVT in the upper leg - Moderate severity; Major bleeding; Quality of life impairment; Time in therapeutic INR range (TTR); Time in therapeutic INR range (TTR); Time in therapeutic INR range (TTR);
SETTING:	Outpatient
PERSPECTIVE:	Clinical recommendation – Population perspective

BACKGROUND: VTE patients receiving a vitamin K antagonist need to keep their INR within the therapeutic target range. If an INR is too low they are at increased risk of VTE, and if it is too high they are at increased risk of bleeding. Therefore an out-of-range INR needs to be corrected by changing the vitamin K antagonist dose. Thereafter a repeat INR measurement is needed to check if the dose correction brought the INR back in the therapeutic range. It is unclear how soon this repeat INR measurement needs to be done.

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	VTE patients receiving a vitamin K antagonist need to keep their INR within the therapeutic target range. If an INR is too low they are at increased risk of VTE, and if it is too high they are at increased risk of bleeding. Therefore an out-of-range INR needs to be corrected by changing the vitamin K antagonist dose. Thereafter a repeat INR measurement is needed to check if the dose correction brought the INR back in the therapeutic range. It is unclear how soon this repeat INR measurement needs to be done.	

DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	For research evidence on Desirable and Undesirable anticipated effects, as well as the certainty of this evidence, see the **Evidence Profile** in the **Appendix**.	
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know		No data was found and panel assumed no harms but more burden. If an INR is drawn too soon (before patient would achieve their steady state on the new dose) the next time interval may be inappropriately prolonged. Too frequent monitoring and too frequent adjustments could increase patient burden and INR instability.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies		

VALUES	**Is there important uncertainty about or variability in 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	**Utility related information - the relative importance of outcomes** *Relative importance of the outcomes on a scale 0.00-1.00 with 1.00 indicating a patient comparing the outcome with being in 'Full health' and 0.00 comparing the outcome with being 'Dead'* <u>Our systematic review found that the relative importance of the outcomes is as follows:</u> - Pulmonary embolism: 0.63-0.93 (different methods)[1-3] - Deep vein thrombosis: 0.64-0.99 (different methods)[1-5] - Deep vein thrombosis patients' own current health: 0.95 (Time trade off)[3] - Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off)[1, 3] - Muscular bleeding: 0.76 (time trade off)[3] - Minor intracranial bleeding event: 0.75 (standard gamble)[1] - Major intracranial bleeding event: 0.15 (standard gamble)[1] - Central nervous system bleeding: 0.29-0.60 (standard gamble)[6, 7] <u>Our survey among ASH guideline panel members found that the relative importance of QoL and TTR is as follows:</u> - Quality of life (QoL) impairment: 0.57 [SD 0.23] (ASH panels utility rating) - Low time in therapeutic range (TTR): 0.74 [SD 0.25] (ASH panels utility rating)	

BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know		Very low quality evidence showed trivial desirable effects and unknown undesirable effects, with possibly important uncertainty or variability in how much people value the outcomes. Reported outcomes only included associations of INR recall interval with time in therapeutic INR range (TTR), not clinical outcomes.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know	**The following economic analyses were identified:** <u>Cost of INR testing</u> In a systematic review, the cost of one INR test was shown to range from $6.19 to $145.70. Cost estimates were based on various combinations of direct medical costs, such as healthcare contacts, equipment, laboratory tests, clerical costs (postage and stationery), telephone calls, quality control, training/education and patient transportation, and indirect costs, such as time lost from work. Of all the included studies, one prospective study in USA reported the cost as $36.32 for patient self-testing and $122.88 for a laboratory test in 2006 US dollars ($43.24 and $146.29 in 2016 US dollars). The estimates included staff time, equipment rental, consumables, phlebotomy and prothrombin time.[8] <u>Cost of clinical events</u> Cost of PE (event cost): $11,616 [9]	The panel also considered additional resource drain by more frequent patient monitoring, e.g. cost of INR recall visit, time off work. Uncertainty about the health outcomes led the panel to judge "Don't know".

		Cost of recurrent VTE (outpatient, hospitalization, and pharmacy cost in 1-year following VTE event): $11,120 [10] Cost of bleeding: [10] - 6 months following DVT: $11,018 for patients with major bleed - Per-event cost estimated over variable follow-up (mean follow-up = 21.3 months): $22,885 for bleed event requiring hospitalization - Per-event cost: base case treatment of bleeds = $9,935 <u>Cost of medication</u> - Warfarin, per month: $15.84 - $51.50 [11]	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies		

COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	The panel could not provide a judgement as health effects are uncertain and no cost-effectiveness analyses were identified.
EQUITY	**What would be the impact on health equity?** ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified.	The panel judged that the requirement of more frequent INR testing likely reduces health equity for patients with transportation or cost barriers.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified.	The following reason was considered by the panel: Patient time commitment for extra INR tests may be a burden and reduce acceptability, but only a small proportion of patients would not return in one week's time.

FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence identified.	The panel judged that a 1 week INR recall interval is feasible as this is widely used in practice.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**	
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or	Probably favors the intervention	Favors the intervention	Varies	**Don't know**	

	JUDGEMENT							IMPLICATIONS
			the comparison					
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**	
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know	

Should a shorter INR recall interval vs. a longer INR recall interval be used following VKA dose adjustment due to an out of target range INR in patients receiving VKA therapy for treatment of VTE?

Type of recommendation

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	●	○	○

Conclusions

RECOMMENDATION	The ASH guideline panel suggests using an INR recall interval of 4 weeks or shorter rather than intervals longer than 4 weeks following VKA dose adjustment due to an out of target range INR in patients receiving treatment for VTE (conditional recommendation based on very low certainty in the evidence).
JUSTIFICATION	Values and preferences: patients are adverse to frequent INR monitoring. The risk of bleeding and thrombosis is low and probably not as important. How much the INR is out of range will guide the choice for the INR recall interval, as well as the etiology of the out of range INR.
SUBGROUP CONSIDERATIONS	No subgroup considerations.
IMPLEMENTATION CONSIDERATIONS	No implementation considerations.
MONITORING AND EVALUATION	No monitoring and evaluation considerations.

RESEARCH PRIORITIES	The following research priority was identified: 1) Low risk of bias studies are required, focusing on critical outcomes and INR instability/variability.

References for Evidence to Decision (EtD) table

1. Hogg K, Kimpton M, Carrier M, Coyle D, Forgie M, Wells P. Estimating quality of life in acute venous thrombosis. JAMA internal medicine. 2013;173(12):1067-72.
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3. Locadia M, Bossuyt PM, Stalmeier PF, Sprangers MA, van Dongen CJ, Middeldorp S, et al. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thrombosis and haemostasis. 2004;92(6):1336-41.
4. Marvig CL, Verhoef TI, de Boer A, Kamali F, Redekop K, Pirmohamed M, et al. Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants. Thrombosis research. 2015;136(1):69-75.
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Appendix - Evidence Profile

Q3. In patients receiving VKA therapy for treatment of VTE should a shorter INR recall interval vs. a longer INR recall interval be used following VKA dose adjustment due to an out of target range INR?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a shorter (e.g. 1 week) INR recall interval following VKA dose adjustment due to an out of target range INR	a longer (e.g. 2-4 weeks) INR recall interval	Relative (95% CI)	Absolute (95% CI)		
Mortality - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
PE - Moderate severity - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
DVT in the upper leg - Moderate severity - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Major bleeding - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Quality of life impairment - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Time in therapeutic INR range (TTR) (follow up: range 8.8 days to 15.6 days; assessed with: Observed minus expected value of site-level time in therapeutic INR range)												
1 [1]	observational studies	not serious	not serious [a]	serious [b,c]	not serious	none			-	NA **0 %** (4.93 lower to 8.55 lower) [d]	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	a shorter (e.g. 1 week) INR recall interval following VKA dose adjustment due to an out of target range INR	a longer (e.g. 2-4 weeks) INR recall interval	Relative (95% CI)	Absolute (95% CI)		
Time in therapeutic INR range (TTR) (follow up: range 6 days to 18 days; assessed with: Observed minus expected value of site-level time in therapeutic INR range)												
1 [1]	observational studies	not serious	not serious [a]	serious [b,c]	not serious	none			-	mean **1.12 lower** (0.8 lower to 1.43 lower) [e]	⨁◯◯◯ VERY LOW	IMPORTANT
Time in therapeutic INR range (TTR) (assessed with: Regression coefficient for the percentage of time in therapeutic range following the change in within center next visit interval)												
1 [2]	observational studies	serious [f]	not serious [a]	serious [c]	not serious	none			-	mean **25.06 lower** (27.84 lower to 22.29 lower) [g]	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval

Explanations

a. Inconsistency cannot be determined as only one study reported this outcome

b. Results only for INR recall interval following high INR values, not low values.

c. The outcome is at the site level, rather than individual patient level.

d. In Rose 2011, there were 37,697 participants with high INR values from 100 sites. INR recall interval and time in therapeutic INR range (TTR) were measured at the site-level. Site performance was measured by calculating observed minus expected (O-E) TTR, whereby a 1% increase indicated that the site performed 1% better than expected according to the risk-adjustment model. This performance in TTR was calculated per quintile for site-level INR recall interval after a high INR, and was 4.20% for Shortest follow-up (mean 8.8 days [95% CI 1.1]), -0.73% for Long follow-up (14.0 [0.4]), and -4.35% for Longest follow-up (15.6 [0.8]). Therefore, compared with Shortest follow-up, Long follow-up had a 4.93% decreased TTR, and Longest follow-up had an 8.55% decreased TTR.

e. In Rose 2011, there were 37,697 participants with high INR values from 100 sites. INR recall interval and time in therapeutic INR range (TTR) were measured at the site-level. Site performance was measured by calculating observed minus expected (O-E) TTR, whereby a 1% increase indicated that the site performed 1% better than expected according to the risk-adjustment model. For each additional day of mean site-level INR recall interval after a high INR, O-E TTR was 1.12% lower (95% CI 0.80 to 1.43%).

f. In this study, the temporal relationship between the test interval and the outcome was unclear. The outcome of time in therapeutic INR range (TTR) itself would have an impact on the determination of the test interval.

g. Tosetto 2015 included 292 centers and 832,204 participants. The site next visit interval (NVI) ratio was estimated as the ratio of days between visits when the INR was below or above range divided by days between visits when the INR was in the therapeutic range (median 0.48; range 0.27-0.97). The adjusted regression coefficient of site level NVI ratio with site-level TTR was -25.06 (95% CI-27.84 to -22.29), which means that per 1 unit increase in NVI the site level TTR decreased by 25.06%.

References – Included Studies

1. Rose AJ, Hylek EM, Berlowitz DR, Ash AS, Reisman JI, Ozonoff A. Prompt repeat testing after out-of-range INR values: a quality indicator for anticoagulation care. Circ Cardiovasc Qual Outcomes. 2011;4(3):276-82.
2. Tosetto A, Manotti C, Marongiu F, Italian Federation of Anticoagulation Clinics clinical quality study g. Center-Related Determinants of VKA Anticoagulation Quality: A Prospective, Multicenter Evaluation. PLoS One. 2015;10(12):e0144314.

Question #4

Should **a longer (6-12 weeks) INR recall interval** vs. **a shorter (4-weeks) INR recall interval** be used **during periods of stable INR control** in **patients receiving maintenance VKA therapy for treatment of VTE**?

POPULATION:	patients receiving maintenance VKA therapy for treatment of VTE	**BACKGROUND:**	VTE patients on a vitamin K antagonist need to keep their INR within the therapeutic target range. Patients who have an INR measurement within the therapeutic range typically need to have their next INR measurement 4 weeks later. However, going to the lab takes time and interferes with the patient's daily activities. Patients who are stable and had their INR within the therapeutic range for a while might benefit from having less frequent INR measurements without increasing their risk for adverse events.
INTERVENTION:	a longer (6-12 weeks) INR recall interval during periods of stable INR control		
COMPARISON:	a shorter (4-weeks) INR recall interval		
MAIN OUTCOMES:	Mortality; PE - Moderate severity; DVT in the upper leg - Moderate severity; Major bleeding; Quality of life impairment; Time in therapeutic INR range (TTR);		
SETTING:	Outpatient		
PERSPECTIVE:	Clinical recommendation – Population perspective		

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	VTE patients on a vitamin K antagonist need to keep their INR within the therapeutic target range. Patients who have an INR measurement within the therapeutic range typically need to have their next INR measurement 4 weeks later. However, going to the lab takes time and interferes with the patient's daily activities. Patients who are stable and had their INR within the therapeutic range for a while might benefit from having less frequent INR measurements without increasing their risk for adverse events.	

DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	For research evidence on Desirable and Undesirable anticipated effects, as well as the certainty of this evidence, see the **Evidence Profile** in the **Appendix**.	Any Thromboembolism only included arterial events (stroke, systemic embolism).
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies		
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability	**Utility related information - the relative importance of outcomes** *Relative importance of the outcomes on a scale 0.00-1.00 with 1.00 indicating a patient comparing the*	

	○ No important uncertainty or variability	*outcome with being in 'Full health' and 0.00 comparing the outcome with being 'Dead'* <u>Our systematic review found that the relative importance of the outcomes is as follows:</u> - Pulmonary embolism: 0.63-0.93 (different methods) [1-3] - Deep vein thrombosis: 0.64-0.99 (different methods) [1-5] - Deep vein thrombosis patients' own current health: 0.95 (Time trade off) [3] - Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) [1, 3] - Muscular bleeding: 0.76 (time trade off) [3] - Minor intracranial bleeding event: 0.75 (standard gamble) [1] - Major intracranial bleeding event: 0.15 (standard gamble) [1] - Central nervous system bleeding: 0.29-0.60 (standard gamble) [6, 7] <u>Our survey among ASH guideline panel members found that the relative importance of QoL and TTR is as follows:</u> - Quality of life (QoL) impairment: 0.57 [SD 0.23] (ASH panels utility rating) - Low time in therapeutic range (TTR): 0.74 [SD 0.25] (ASH panels utility rating)	

BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		Very low quality evidence showed small desirable effects and trivial undesirable effects, with possibly important uncertainty or variability in how much people value the outcomes.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know	**The following economic analyses were identified:** <u>Cost of INR testing</u> In a systematic review, the cost of one INR test was shown to range from $6.19 to $145.70. Cost estimates were based on various combinations of direct medical costs, such as healthcare contacts, equipment, laboratory tests, clerical costs (postage and stationery), telephone calls, quality control, training/education and patient transportation, and indirect costs, such as time lost from work. Of all the included studies, one prospective study in USA reported the cost was $36.32 for patient self-test and $122.88 for a laboratory test in 2006 US dollar ($43.24 and $146.29 in 2016 US dollar). The estimates included staff time, equipment rental, consumables, phlebotomy and PT time. [8] <u>Cost of clinical events</u> Cost of PE (event cost): $11,616 [9]	

		Cost of recurrent VTE (outpatient, hospitalization, and pharmacy cost in 1-year following VTE event): $11,120 [10] Cost of bleeding: [10] - 6 months following DVT: $11,018 for patients with major bleed - Per-event cost estimated over variable follow-up (mean follow-up = 21.3 months): $22,885 for bleed event requiring hospitalization - Per-event cost: base case treatment of bleeds = $9,935 <u>Cost of medication</u> - Warfarin, per month: $15.84 - $51.50 [11]	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ● Low ○ Moderate ○ High ○ No included studies		

COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	The panel could not provide a judgement as no cost-effectiveness analyses were identified.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ● Increased ○ Varies ○ Don't know	No research evidence identified.	The panel judged that the intervention increases health equity for patients with transportation barriers.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence identified.	The following reason was considered by the panel: The intervention will be acceptable for all key stakeholders.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	A prospective evaluation of a 12-week INR follow-up interval in Veterans receiving a stable dose of warfarin found that only 56% achieved a 12-week follow-up interval and only 34% maintained a 12-week follow-up interval during 6 months. [12]	The panel judged that implementation of the intervention is feasible in any setting.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know	
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies	

	JUDGEMENT							IMPLICATIONS
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	**Increased**	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know	

Should a longer (6-12 weeks) INR recall interval vs. a shorter (4-weeks) INR recall interval be used during periods of stable INR control in patients receiving maintenance VKA therapy for treatment of VTE?

Type of recommendation

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○

Conclusions

RECOMMENDATION	The ASH guideline panel suggests using a longer (6-12 weeks) INR recall interval rather than a shorter (4-weeks) INR recall interval during periods of stable INR control in patients receiving maintenance VKA therapy for treatment of VTE (conditional recommendation based on very low certainty in the evidence). Remarks: This recommendation would apply to patients whose anticoagulation is being monitored and followed by health care providers. This may not apply to patients using self-testing (PST) or self-management (PSM), who may require different INR recall intervals.
JUSTIFICATION	Based on the body of available evidence, there is very low certainty that there is an effect of 6 to 12 week INR recall intervals on clinically important outcomes, but there is also no evidence of harm. However, because of very low certainty of evidence, and no published information about recurrent VTE outcomes, the fact that we did not find evidence of an effect on these outcomes does not imply that such an effect does not exist. The panel felt a conditional recommendation for this intervention was reasonable because less frequent INR monitoring reduces burden on patients, lessens workload on providers, is acceptable to key stakeholders, and is feasible to implement.
SUBGROUP CONSIDERATIONS	No subgroup considerations.
IMPLEMENTATION CONSIDERATIONS	The panel did not specify a definition of stable INR control and felt that this should be defined according to local standards. The panel also determined that this recommendation should not be used for patients engaging in PST or PSM as these patients are usually monitored more frequently than the 4 week INR recall interval comparator used for this recommendation. Patients should be instructed to have their INR tested anytime their health status changes, their current medications change, or there is a significant change in their dietary intake of vitamin K containing foods.
MONITORING AND EVALUATION	No monitoring and evaluation considerations.
RESEARCH PRIORITIES	The panel identified the following additional research questions: 1) What is the comparative effectiveness of 6 to 12 week INR recall intervals compared to a 4 week recall interval in real-world patients during periods of stable INR control? Given the low risk of adverse events in stable patients, a very large patient sample will likely be required to answer this question. 2) What is the cost-effectiveness of 6 to 12 week INR recall intervals compared to a 4 week recall interval from the societal perspective?

References for Evidence to Decision (EtD) table

1. Hogg K, Kimpton M, Carrier M, Coyle D, Forgie M, Wells P. Estimating quality of life in acute venous thrombosis. JAMA internal medicine. 2013;173(12):1067-72.
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6. Lenert LA, Soetikno RM. Automated computer interviews to elicit utilities: potential applications in the treatment of deep venous thrombosis. Journal of the American Medical Informatics Association : JAMIA. 1997;4(1):49-56.
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9. Saunders RJ, Ozols AA. Cost burden of venous thromboembolism and its prophylaxis in the United States. 2016.
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12. Porter AL, Margolis AR, Schoen RR, Staresinic CE, Ray CA, Fletcher CD. Use of an extended INR follow-up interval for Veteran patients in an anticoagulation clinic. J Thromb Thrombolysis. 2017;43(3):318-25.

Appendix – Evidence Profile

Q4. In patients receiving maintenance VKA therapy for treatment of VTE should a longer (6-12 weeks) INR recall interval vs. a shorter (4-weeks) INR recall interval be used during periods of stable INR control?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**a longer (6-12 weeks) INR recall interval during periods of stable INR control**	**a shorter (4-weeks) INR recall interval**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality (follow up: range 12 months to 2 years)												
2 [1, 2]	randomised trials	not serious [a]	not serious	serious [b,c]	very serious [d]	none	3/183 (1.6%)	3.9% [e]	RR 0.73 (0.12 to 4.60)	**11 fewer per 1,000** (from 34 fewer to 140 more)	⨁◯◯◯ VERY LOW	CRITICAL
PE - Moderate severity (follow up: mean 12 months; assessed with: Thromboembolism)												
2 [1, 2]	randomised trials	not serious	not serious	serious [b,c,f]	very serious [d]	none	0/183 (0.0%)	2.0% [e]	RR 0.27 (0.03 to 2.41)	**15 fewer per 1,000** (from 19 fewer to 28 more)	⨁◯◯◯ VERY LOW	CRITICAL
DVT in the upper leg - Moderate severity (follow up: mean 12 months; assessed with: Thromboembolism)												
2 [1, 2]	randomised trials	not serious	not serious	serious [b,c,f]	very serious [d]	none	0/183 (0.0%)	2.6% [e]	RR 0.27 (0.03 to 2.41)	**19 fewer per 1,000** (from 25 fewer to 37 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**a longer (6-12 weeks) INR recall interval during periods of stable INR control**	**a shorter (4-weeks) INR recall interval**	**Relative (95% CI)**	**Absolute (95% CI)**		
Major bleeding (follow up: range 12 months to 2 years)												
2 [1, 2]	randomised trials	not serious	not serious	not serious [b,c]	very serious [d]	none	5/183 (2.7%)	1.7% [e,g]	RR 1.05 (0.30 to 3.65)	**1 more per 1,000** (from 12 fewer to 45 more)	⊕⊕◯◯ LOW	CRITICAL
								2.1% [e,g]		**1 more per 1,000** (from 15 fewer to 56 more)		
Quality of life impairment - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Time in therapeutic INR range (TTR) (follow up: mean 12 months; assessed with: Percentage of time in the therapeutic INR range (TTR))												
1 [2]	randomised trials	not serious	not serious [h]	serious [c]	serious [i]	none	124	126	-	MD **2.5 % lower** (7.3 lower to 2.3 higher)	⊕⊕◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Mortality is not likely to be biased

b. Pengo 2003 only included patients with a prosthetic mechanical heart valve (target INR, 3.0) and assessed the effect of a 6 weeks interval instead of 12 weeks. [1]

c. Schulman 2011 included patients from an anticoagulation clinic, primarily with other indications that VTE (atrial fibrillation, heart valve replacement). [2]

d. Lower and upper bounds of the 95% CI for the anticipated absolute effect include important benefit and important harm.

e. Median annual risk among 11 RCTs comparing LMWH/VKA with DOAC in patients requiring treatment for VTE.[3-13] This risk was observed in the original trial at 6 months and to obtain the annual risk, we assumed a linear increase over time and doubled the risk observed at 6 months. See also the ASH guideline on Treatment of VTE

f. Outcome of any thromboembolism captured only arterial events

g. High bleeding risk of 2.1% in patients treated with anticoagulants for 6 months, from a systematic review of 13 prospective cohort studies and 56 randomized trials.[14] See also the ASH guideline on Treatment of VTE

h. Inconsistency cannot be determined as only one RCT reported the outcome [2]

i. Lower and upper bounds of the 95% CI for the anticipated absolute effect include benefit and important harm

References – Included RCTs

1. Pengo V, Barbero F, Biasiolo A, Pegoraro C, Cucchini U, Iliceto S. A comparison between six- and four-week intervals in surveillance of oral anticoagulant treatment. Am J Clin Pathol. 2003;120(6):944-7.
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Question#5

Should **specialized anticoagulation management service care** vs. **care provided by the patient's physician** be used **for anticoagulation management** in **patients receiving anticoagulation therapy for treatment of VTE**?

POPULATION:	patients receiving anticoagulation therapy for treatment of VTE
INTERVENTION:	specialized anticoagulation management service care
COMPARISON:	care provided by the patient's physician
MAIN OUTCOMES:	Mortality; PE - Moderate severity; DVT in the upper leg - Moderate severity; Major bleeding; Quality of life impairment; Time in therapeutic INR range; Inadequate medication adherence for DOACs;
SETTING:	Inpatient and outpatient
PERSPECTIVE:	Clinical recommendation - Population perspective

BACKGROUND: Anticoagulants need to be managed well in order to achieve their optimal therapeutic benefit. Vitamin K antagonists need to be kept within the therapeutic range, LMWH might need to be monitored, and all patients on an oral anticoagulant including DOAC need to adhere to their prescribed treatments. A specialized clinic with personnel and management tools specifically for managing patients on anticoagulation might improve the quality of anticoagulation management and thereby patient outcomes.

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Anticoagulants need to be managed well in order to achieve their optimal therapeutic benefit. Vitamin K antagonists need to be kept within the therapeutic range, LMWH might need to be monitored, and all patients on an oral anticoagulant including DOAC need to adhere to their prescribed treatments. A specialized clinic with personnel and management tools specifically for managing patients on anticoagulation might improve the quality of anticoagulation management and thereby patient outcomes.	

DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	For research evidence on Desirable and Undesirable anticipated effects, as well as the certainty of this evidence, see the **Evidence Profile** in the **Appendix**.	
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies		
VALUES	**Is there important uncertainty about or variability in 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	**Utility related information - the relative importance of outcomes** *Relative importance of the outcomes on a scale 0.00-1.00 with 1.00 indicating a patient comparing the outcome with being in 'Full health' and 0.00 comparing the outcome with being 'Dead'*	Patient representatives: views were expressed that primary care providers may be better informed about patients' other medical issues and therefore patients may prefer

		<u>Our systematic review found that the relative importance of the outcomes is as follows:</u> - Pulmonary embolism: 0.63-0.93 (different methods)[1-3] - Deep vein thrombosis: 0.64-0.99 (different methods)[1-5] - Deep vein thrombosis patients' own current health: 0.95 (Time trade off)[3] - Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off)[1, 3] - Muscular bleeding: 0.76 (time trade off)[3] - Minor intracranial bleeding event: 0.75 (standard gamble)[1] - Major intracranial bleeding event: 0.15 (standard gamble)[1] - Central nervous system bleeding: 0.29-0.60 (standard gamble)[6, 7] <u>Our survey among ASH guideline panel members found that the relative importance of QoL, TTR and medication adherence is as follows:</u> - Quality of life (QoL) impairment: 0.57 [SD 0.23] (ASH panels utility rating) - Low time in therapeutic range (TTR): 0.74 [SD 0.25] (ASH panels utility rating) - Inadequate medication adherence: 0.76 [SD 0.26] (ASH panels utility rating)	anticoagulation management by their primary care provider, if travel to the clinic and other inconveniences were the same.

BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		Very low quality evidence showed small desirable effects and trivial undesirable effects, with possibly important uncertainty or variability in how much people value the outcomes.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**The following economic analyses were identified:** <u>Cost of specialized anticoagulation management services</u> Incremental cost of pharmacist-managed anticoagulation service follow-up compared with physician care was estimated at $123.80 CAD per patient year.[8] Mean costs per patient year of warfarin monitoring in three AMS settings ranged from $216 to $339. [9] Cost of AMS service $15.00 per month.[10] Total operational cost of the AMS was $2.10 per patient per day.[11] 5-year medical care and patient/caregiver costs per 100 patients was $529,737 in usual care and $645,671 in ACC. The direct medical cost per patient-year of AMS and regular care were $840 and $1,179, respectively.[12] <u>Cost of clinical events</u> Cost of PE (event cost): $11,616 [13] Cost of recurrent VTE (outpatient, hospitalization, and pharmacy cost in 1-year following VTE event): $11,120 [14] Cost of bleeding[14]	

		- 6 months following DVT: $11,018 for patients with major bleed - Per-event cost estimated over variable follow-up (mean follow-up = 21.3 months): $22,885 for bleed event requiring hospitalization - Per-event cost: base case treatment of bleeds = $9,935 <u>Cost of medications</u>[15] - Warfarin, per month: $15.84 - $51.50 - DOAC, per month: $300.42 - $600.88 - UFH, per week: $37.00 - LMWH, per week: $199.92 - $712.00	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies		

COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	**The following cost-effectiveness analyses were identified:** AMS was estimated to have a cost savings in reduced hospitalizations and ED visits of $162,058 per 100 patients annually as compared to usual care.[16] Potential cost avoidance by prevention of hospitalizations and ED visits for anticoagulation complications was $4,072.68 per person year.[10] Probabilistic sensitivity analyses demonstrated that AMS was cost-effective more than 79% of the time from both patient and healthcare provider perspectives at a willingness-to-pay threshold of SG$69,050 (€62,701) per QALY.[17] When only considering all the costs of each treatment, moving from usual care to AMS resulted in a cost-effectiveness ratio of $31,327 per avoided event.[12] Taking into account the costs associated with the emergency department, hospitalizations and staff services, the anticoagulation service lead to a total net savings of $241,400 per 100 patients-year.[18] Cost-effectiveness of the patient-paid pharmacist- assisted warfarin monitoring service: the patient-paid pharmacist-assisted warfarin monitoring program resulted in an average of 0.13 QALYs gained and a cost increment of $1,683 per person compared to usual care. The incremental cost-effectiveness ratio (ICER) was $12,837 per QALY gained.[19]	Very low quality evidence, studies typically did not consider upfront costs of setting up a specialized anticoagulation management service.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know	No research evidence identified.	The panel judged that the direction or impact on health equity is uncertain for the following reasons: The presence of the AMS might make general practitioners more confident to prescribe anticoagulation and refer patients to the

			AMS for management. On the other hand, if the AMS is situated in a hospital, rural patients' out-of-pocket costs for visits might be higher. This could be addressed by the use of telehealth. Further, patients who are referred by the general practitioner but are not attending the AMS might be different, such as higher risk for clinical events.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Observational evidence showed the following acceptability and satisfaction among key stakeholders:** <u>Patients</u> One RCT sub-analysis including patients who had received care in an AMS and outside an AMS by a family physician preferred to receive AMS care.[20] Two observational studies among patients receiving pharmacist-managed AMS care were accepting of management by a pharmacist.[21, 22] One RCT sub-analysis showed no difference in General treatment satisfaction between patients receiving AMS care vs. no AMS care (change score difference 0.1 [-0.2 - 0.4]).[8] One RCT sub-analysis showed that 96% of patients in the anticoagulation clinic group were either very satisfied or satisfied with their overall warfarin care compared with 84% of patients in the family physician group.[23] One observational study showed that treatment satisfaction was extremely high among AMS patients.[24] <u>Providers</u>	The following reasons were considered by the panel: AMS seem to be acceptable for patients and providers. It is unknown if hospital administrators are willing to dedicate funds to setting up and running an AMS, also considering that DOAC management requires an AMS to a lesser extent.

		Two observational studies on pharmacist-managed AMS care showed that the pharmacists involved were receptive to and confident in managing patients on anticoagulation.[21, 22] Pharmacists felt sufficiently competent to manage anticoagulation patients with the assistance of a protocol, training and feedback.[25] One observational study showed that provider (medical, nursing, and administrative staff) satisfaction with the AMS service was extremely high.[24]	
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Observational studies showed the following financial and non-financial barriers to utilizing the intervention:** <u>Financial</u> Mean patient cost for AMS visits highly varies between countries, and in most countries the time cost (time lost on work or leisure) was the main driver.[26] Patient cost of attending an AMS in secondary care was twice as high compared with attending an AMS in primary care.[27] <u>Non-Financial</u> Time limitation was identified by pharmacists in the specialized service as a major barrier to self-perceived quality of care and expansion of the service beyond the hospitalist group.[25] One observational study among AMS personnel showed that many reported barriers to measuring complication rates and extrapolating standards from the literature.[28] One observational study showed that it is feasible to implement an AMS in a rural setting and achieve similar quality of care as in resource-rich settings.[29] Using a point-of-care INR device and reporting INR to the clinic reduces the INR processing time.[30] A nurse-led AMS with computer decision support is feasible to implement.[31]	The panel considered that in low income settings the use of telehealth and other specifics may improve access and reduce cost.

		Pharmacist POC INR testing is well correlated with laboratory INR measurement.[21] An AMS may achieve a similar TTR with a simple algorithm as with computer decision support.[32] Most primary care physicians dose anticoagulation based on expertise or a manual algorithm, and few experienced problems.[22] An interim telephone follow-up with patients may not improve TTR in an AMS.[33]	

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know	
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability				

	JUDGEMENT							IMPLICATIONS
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**	
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Should specialized anticoagulation management service care vs. care provided by the patient's physician be used for anticoagulation management in patients receiving anticoagulation therapy for treatment of VTE?

Type of recommendation

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○

Conclusions

RECOMMENDATION	The ASH guideline panel suggests using specialized anticoagulation management service care rather than care provided by the patient's physician in patients receiving treatment for VTE (conditional recommendation based on very low certainty in the evidence).
JUSTIFICATION	Very low quality evidence pointed to small desirable anticipated effects and only trivial undesirable anticipated effects. The intervention is probably cost-effective, acceptable and feasible.
SUBGROUP CONSIDERATIONS	The recommendation mainly applies to patients on VKA as all but two of the studies focused on VKA treatment. AMS may be most effective when implemented in a population managed by non-specialized providers with a very low time in therapeutic INR range.
IMPLEMENTATION CONSIDERATIONS	Decision makers should consider the upfront costs of setting up the AMS as well as costs to maintain the clinic. The AMS can also provide specialized consulting and education for practitioners in the region, thereby potentially enhancing anticoagulation management beyond the clinic's performance.

MONITORING AND EVALUATION	AMS should keep track of the time in therapeutic INR range as well as anticoagulation-related clinical events for their patients. Physicians referring patients to an AMS should keep track of whether they attended the clinic.
RESEARCH PRIORITIES	RCT evidence needs to be strengthened to be considered superior to the reported observational evidence. Cluster RCTs are needed that are appropriately randomized, enroll patients before (unblinding of) allocation, and are sufficiently powered to detect a difference in clinical outcomes using blinded outcome assessment, including the follow-up time after dropping out of anticoagulation care.

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Appendix – Evidence Profile

Q5. In patients receiving anticoagulation therapy for treatment of VTE should specialized anticoagulation management service care vs. care provided by the patient's physician be used for anticoagulation management?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**specialized anticoagulation management service care**	**no specialized anticoagulation management service care provided by the patient's physician**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality (follow up: range 90 days to 1 years)												
5 [1-5]	observational studies	serious [a]	not serious	serious [b]	serious [c]	none	16/4298 (0.4%)	23/4468 (0.5%) [d]	RR 0.97 (0.51 to 1.85)	**0 fewer per 1,000** (from 3 fewer to 4 more)	⊕◯◯◯ VERY LOW	CRITICAL
								3.9% [d]		**1 fewer per 1,000** (from 19 fewer to 33 more)		
PE - Moderate severity (follow up: range 6 days to 2 years; assessed with: Any thromboembolism)												
18 [1-18]	observational studies	serious [a]	not serious	serious [b]	not serious	strong association	51/5817 (0.9%)	146/6852 (2.1%) [d]	RR 0.45 (0.26 to 0.78)	**12 fewer per 1,000** (from 5 fewer to 16 fewer)	⊕◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**specialized anticoagulation management service care**	**no specialized anticoagulation management service care provided by the patient's physician**	**Relative (95% CI)**	**Absolute (95% CI)**		
								2.0% [d]		**11 fewer per 1,000** (from 4 fewer to 15 fewer)		
DVT in the upper leg - Moderate severity (follow up: range 6 days to 2 years; assessed with: Any thromboembolism)												
18 [1-18]	observational studies	serious [a]	not serious	serious [b]	not serious	strong association	51/5817 (0.9%)	146/6852 (2.1%) [d]	RR 0.46 (0.26 to 0.78)	**12 fewer per 1,000** (from 5 fewer to 16 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
								2.6% [d]		**14 fewer per 1,000** (from 6 fewer to 19 fewer)		
Major bleeding (follow up: range 6 days to 2 years)												
19 [1-19]	observational studies	serious [a]	not serious	not serious	serious [c]	none	113/5852 (1.9%)	307/6887 (4.5%) [d,e]	RR 0.66 (0.42 to 1.03)	**15 fewer per 1,000** (from 1 more to 26 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**specialized anticoagulation management service care**	**no specialized anticoagulation management service care provided by the patient's physician**	**Relative (95% CI)**	**Absolute (95% CI)**		
								1.7% [d,e]		**6 fewer per 1,000** (from 1 more to 10 fewer)		
								2.1% [d,e]		**7 fewer per 1,000** (from 1 more to 12 fewer)		
Quality of life impairment (follow up: mean 30 days; assessed with: EuroQoL)												
1 [20]	randomised trials	very serious [g]	not serious [h]	serious [b]	not serious	none	EuroQoL change score from baseline to follow up was the same in both groups with 0.1 (0.2), and the difference in the mean change score was −0.01 (−0.07 to 0.05)				⊕◯◯◯ VERY LOW	CRITICAL
Time in therapeutic INR range (follow up: range 30 days to 2 years; assessed with: Mean TTR; Scale from: 0 to 100)												
19 [1, 4-6, 8, 10, 12-16, 18, 21-26]	observational studies	serious [a]	not serious	not serious	not serious	none	5691	6188	-	MD **3.51 % higher** (2.74 higher to 4.28 higher)	⊕◯◯◯ VERY LOW	IMPORTANT
Inadequate medication adherence for DOACs (follow up: range 3 months to 6 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	specialized anticoagulation management service care	no specialized anticoagulation management service care provided by the patient's physician	Relative (95% CI)	Absolute (95% CI)		
2 [9, 27]	observational studies	serious [i]	not serious [h]	serious [j]	not serious	none	At the site level (4863 patients from 41 sites): appropriate patient selection (RR,1.14; 95% CI, 1.05-1.25), and provision of pharmacist-led monitoring (RR,1.25; 95% CI, 1.11–1.41) were associated with better patient adherence to dabigatran, but pharmacist-led education was not (RR,0.94; 95% CI, 0.83-1.06). (Shore 2015) Fewer dabigatran patients managed in an anticoagulation clinic (total N=20) were non-adherent compared with usual care patients (total N=48), but this was not statistically significant (10% vs. 25%; p=0.16) (Lee 2013)				⊕◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Most studies did not provide an adjusted analysis and were at risk of confounding, and many were Before-After studies

b. Most study populations represented a mix of indications for anticoagulation, whereby typically a minority had VTE as indication

c. Lower and upper bounds of the 95% CI for the anticipated absolute effect include important benefit and important harm

d. Median annual risk among 11 RCTs comparing LMWH/VKA with DOAC in patients requiring treatment for VTE. [28-38] This risk was observed in the original trial at 6 months and to obtain the annual risk, we assumed a linear increase over time and doubled the risk observed at 6 months. See also the ASH guideline on Treatment of VTE

e. High bleeding risk of 2.1% in patients treated with anticoagulants for 6 months, from a systematic review of 13 prospective cohort studies and 56 randomized trials.[39] See also the ASH guideline on Treatment of VTE

f. Subjective outcome with lack of blinding

g. Inconsistency cannot be determined as only one study (Lalonde 2008) reported quality of life [20]

h. One small underpowered study (Lee 2013) and one retrospective association study [27]

i. Not a direct comparison, but association at the site-level. Study only included in atrial fibrillation patients [27]

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Question #6

Should **point-of-care INR testing by the patient at home (patient self-testing; PST)** vs. **any other INR testing approach** be used in **patients receiving maintenance VKA therapy for treatment of VTE**?

POPULATION:	patients receiving maintenance VKA therapy for treatment of VTE
INTERVENTION:	point-of-care INR testing by the patient at home (patient self-testing; PST)
COMPARISON:	any other INR testing approach
MAIN OUTCOMES:	Mortality; Pulmonary Embolism - Moderate; Deep Venous Thrombosis in the Upper Leg - Moderate; Major Bleeding; Quality of Life; Time in Therapeutic INR Range;
SETTING:	Outpatient
PERSPECTIVE:	Clinical recommendation - Population perspective

BACKGROUND: Patients using a vitamin K antagonist for VTE treatment need to keep the International Normalized Ratio (INR) within the therapeutic range in order to achieve an optimal balance between the risk of VTE recurrence and bleeding. To achieve this, the INR needs to be monitored in order to decide whether a dose change is needed. To monitor their INR patients have to go to a laboratory or clinical office on a regular basis. Patient self-testing (PST) at home could reduce the treatment burden on the patient, and by actively engaging the patient in monitoring PST might improve clinical outcomes.

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Patients using a vitamin K antagonist for VTE treatment need to keep the International Normalized Ratio (INR) within the therapeutic range in order to achieve an optimal balance between the risk of VTE recurrence and bleeding. To achieve this, the INR needs to be monitored in order to decide whether a dose change is needed. To monitor their INR patients have to go to a laboratory or clinical office on a regular basis. Patient self-testing (PST) at home could reduce the treatment burden on the patient, and by actively engaging the patient in monitoring PST might improve clinical outcomes.	

DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	For research evidence on Desirable and Undesirable anticipated effects, as well as the certainty of this evidence, see the **Evidence Profile** in the **Appendix**.	All health effects in the same direction.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ● Low ○ Moderate ○ High ○ No included studies		Mortality evidence was of High certainty, while evidence for all other outcomes had Low certainty.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability	**Utility related information - the relative importance of outcomes**	

	○ No important uncertainty or variability	*Relative importance of the outcomes on a scale 0.00-1.00 with 1.00 indicating a patient comparing the outcome with being in 'Full health' and 0.00 comparing the outcome with being 'Dead'* <u>Our systematic review found that the relative importance of the outcomes is as follows:</u> - Pulmonary embolism: 0.63-0.93 (different methods)[1-3] - Deep vein thrombosis: 0.64-0.99 (different methods)[1-5] - Deep vein thrombosis patients' own current health: 0.95 (Time trade off)[3] - Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off)[1, 3] - Muscular bleeding: 0.76 (time trade off)[3] - Minor intracranial bleeding event: 0.75 (standard gamble)[1] - Major intracranial bleeding event: 0.15 (standard gamble)[1] - Central nervous system bleeding: 0.29-0.60 (standard gamble)[6, 7] <u>Our survey among ASH guideline panel members found that the relative importance of QoL and TTR adherence is as follows:</u> - Quality of life (QoL) impairment: 0.57 [SD 0.23] (ASH panels utility rating) - Low time in therapeutic range (TTR): 0.74 [SD 0.25] (ASH panels utility rating)	

BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		Low quality evidence showed small desirable effects and trivial undesirable effects, with possibly important uncertainty or variability in how much people value the outcomes.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**The following economic analyses were identified:** <u>Cost of patient self-testing</u> The total cost per patient over 2 years of follow-up was $32,484 for anticoagulation clinic and $33,460 for weekly PST, representing a difference of $976.[8] On a per patient basis over a 6 month period, PST resulted in an incremental cost of €59.08 in comparison with routine care.[9] <u>Cost of clinical events</u> Cost of PE (event cost): $11,616 [10] Cost of recurrent VTE (outpatient, hospitalization, and pharmacy cost in 1-year following VTE event): $11,120 [11] Cost of bleeding:[11] - 6 months following DVT: $11,018 for patients with major bleed - Per-event cost estimated over variable follow-up (mean follow-up = 21.3 months): $22,885 for bleed event requiring hospitalization - Per-event cost: base case treatment of bleeds = $9,935	Cost of the intervention was thought to be higher than the cost of usual care in the real world and results of these two studies (Phibbs 2016, Gallagher 2015) may not be reflective of the real life setting.

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ● Low ○ Moderate ○ High ○ No included studies		Two RCTs evaluated cost. Indirectness was one of the primary concerns.
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	**The following cost-effectiveness analyses were identified:** One review, one RCT and one modeling study showed that PST is likely to be cost-effective compared with usual care:[8, 12, 13] - The Sharma 2015 review showed that in the UK setting total health and social care costs over 10 years were £7,324 with standard care and £7,326 with self-monitoring (estimated QALY gain was 0.028). Self-monitoring was found to have ~80% probability of being cost-effective compared with standard care applying a ceiling willingness-to-pay threshold of £20,000 per QALY gained [12] - The Phibbs 2016 RCT showed that in the USA setting the incremental cost per QALY gained with PST once weekly was $5,566 USD (95 % CI, −$11,490 to $25,142). The ICER for weekly PST versus anticoagulation clinic was well within accepted standards for cost-effectiveness, and was preferred over more or less frequent PST [8] - The Stefanovic 2016 modeling study showed that in the Dutch setting, increasing PST and/or PSM usage in the national cohort from the current 15.4% to 50% resulted in savings ranging from €8 million after the first year to €184 million after 5 years. Unfavorable budget impact was found in scenarios exploring an increase in the use of PST alone as well as an increase in the market share of PST and PSM in patients with atrial fibrillation [13] However, three other reviews showed that PST is unlikely to be cost-effective within accepted standards:[14-16]	Reasons for differences in findings between identified cost-effectiveness studies are not completely clear. Depending on the setting and intensity of the intervention, as well as the duration of therapy, cost-effectiveness will differ. Therefore, the panel chose "Varies". Most of the available evidence is from mixed populations (including atrial fibrillation and mechanical heart valves) and that increases indirectness for the VTE population.

		- The CADTH 2014 analysis showed that in the Canadian setting PST was more costly compared with laboratory testing of INR and unlikely to be cost-effective [14] - The HQO 2009 analysis showed that in the Ontario setting PST was just as effective as conventional laboratory-based INR testing for thromboembolic events, major hemorrhages, and all-cause mortality [16] - The Connock 2007 review showed that in the UK setting the incremental cost per QALY gained by patient PST is £122,365 over 5 years and £63,655 over 10 years. In general, PST is unlikely to be more cost-effective than the current specialised anticoagulation clinics in the UK, but PST may enhance the quality of life for some patients [15]	
EQUITY	**What would be the impact on health equity?** ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	One observational study showed that successful home monitoring of prothrombin with a PST device required adequate levels of cognition and manual dexterity. Training a caregiver modestly increased the proportion of patients who can perform PST.[17] One observational study showed that patients living farther away from the anticoagulation clinic did not benefit to a larger extent than patients living close to the clinic, and restricting access to patients living farther away is not likely to improve cost-effectiveness of PST.[18]	The intervention is likely to reduce equity because of affordability, ability to use self-testing equipment adequately. Although self-testing will reduce time commitment and cost of traveling to the laboratory/clinic, restricting PST to patients living more than a certain distance from the ACC is not likely to improve its cost-effectiveness. From a practical perspective for patients who are not able to be treated with VKA (including those who are unable to be tested or test themselves) are likely to be on DOACs. For patients who cannot receive DOACs, anticoagulation clinics are an option but people living in remote areas

			are less likely to be able to access these clinics. A patient representative's wished home testing was an option, but one barrier is the requirement to be stable in the therapeutic range for at least 3 to 6 months. The panel agreed to say 'Probably reduced' with the exception of a few scenarios.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	**Observational evidence showed the following acceptability and concerns among key stakeholders:** <u>Patients</u> Among patients who were offered or tried PST, most preferred point-of-care self-testing over laboratory testing.[19-23] <u>Healthcare providers</u> Providers are generally positive about PST. Concerns include unintended self-management and the need for quality assurance of the point-of-care device.[24]	The panel considered the following for the judgement: For some patients PST is not an acceptable option because they do not want to perform the testing, others would. Payers might not want to cover the costs in all settings.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Observational studies showed the following non-financial barriers to utilizing the intervention:** <u>Non-financial barrier</u> Quality assurance of the point-of-care devices is needed to maintain PST safe and reliable.[24]	The panel considered the following for the judgement: The intervention is feasible for patients who are able to perform PST and are struggling to perform INR monitoring with usual care, but it

			requires substantial reorganization in some settings. Sustainability of the intervention is of concern, because of the possible budget impact. The panel discussed that the intervention is feasible in certain settings, e.g. in countries with national networks of anticoagulation clinics such as Sweden. The panel judged 'Probably yes', but resources need to be invested.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies	

	JUDGEMENT							IMPLICATIONS
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies	
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Should point-of-care INR testing by the patient at home (patient self-testing; PST) vs. any other INR testing approach be used in patients receiving maintenance VKA therapy for treatment of VTE?

Type of recommendation

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○

Conclusions

RECOMMENDATION	The ASH guideline panel suggests using home point-of-care INR testing (patient self-testing; PST) over any other INR testing approach except for patient self-management (PSM) in suitable patients (those with demonstrated competency to perform PST and can afford this option) receiving maintenance VKA therapy for treatment of VTE (conditional recommendation based on low certainty in the evidence).
JUSTIFICATION	This benefit is conditional upon patients and healthcare systems being able to afford and manage the self-testing equipment, and therefore probably applies to a relatively small percentage of eligible patients. In settings where resources are limited or when patients are not willing or able to perform PST, deviation from this recommendation is appropriate.
SUBGROUP CONSIDERATIONS	The recommendation applies to patients in whom providers believe that valid results can be obtained, i.e. in patients on extended (indefinite) anticoagulation who are able to perform and afford PST.
IMPLEMENTATION CONSIDERATIONS	Systems using PST should be able to ensure quality assurance of the testing equipment and patient's ability to obtain accurate INR results.

	The panel considered that a potential benefit of alternative care options is that loss to follow up appears less likely compared to PST as patients would have to return to clinics more frequently. The panel considered that lack of awareness of PST by primary care providers is a potential barrier. The panel calls upon payers to carefully evaluate current reimbursement regulations and make changes as necessary to ensure that providers and patients are aware of this testing option, while also ensuring that unnecessary testing is not incentivized.
MONITORING AND EVALUATION	No monitoring and evaluation considerations.
RESEARCH PRIORITIES	The panel identified the following additional research questions: 1) What is the comparative effectiveness of PST compared to other INR testing strategies specifically in patients with VTE? 2) What is the comparative effectiveness of PST compared to DOAC therapy?

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Appendix – Evidence Profile

Q6. In patients receiving maintenance VKA therapy for treatment of VTE should point-of-care INR testing by the patient at home (patient self-testing; PST) vs. any other INR testing approach be used?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**INR point-of-care testing by the patient at home (PST)**	**any other INR testing approach**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality (follow up: range 6 months to 57 months)												
3 [1-5]	randomised trials	not serious	not serious	not serious	not serious	none	173/1678 (10.3%)	3.9% [a]	RR 0.94 (0.77 to 1.14)	**2 fewer per 1,000** (from 5 more to 9 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Pulmonary Embolism - Moderate (follow up: range 3 months to 57 months; assessed with: Thromboembolic events)												
9 [1-10]	randomised trials	serious [b]	not serious	not serious	serious [c]	none	54/2188 (2.5%)	2.0% [a]	RR 0.73 (0.52 to 1.03)	**5 fewer per 1,000** (from 1 more to 10 fewer)	⊕⊕◯◯ LOW	CRITICAL
Deep Venous Thrombosis in the Upper Leg - Moderate (follow up: range 3 months to 57 months; assessed with: Thromboembolic Events)												
9 [1-10]	randomised trials	serious [b]	not serious	not serious	serious [c]	none	54/2188 (2.5%)	2.6% [a]	RR 0.73 (0.52 to 1.03)	**7 fewer per 1,000** (from 1 more to 12 fewer)	⊕⊕◯◯ LOW	CRITICAL
Major Bleeding (follow up: range 3 months to 57 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	INR point-of-care testing by the patient at home (PST)	any other INR testing approach	Relative (95% CI)	Absolute (95% CI)		
9 [1-10]	randomised trials	serious [b]	not serious	not serious	serious [d]	none	174/2188 (8.0%)	1.7% [a,e]	RR 0.73 (0.46 to 1.15)	**5 fewer per 1,000** (from 3 more to 9 fewer)	⊕⊕◯◯ LOW	CRITICAL
								2.1% [a,e]		**6 fewer per 1,000** (from 3 more to 11 fewer)		
Quality of Life (follow up: mean 2 years)												
1 [2, 3]	randomised trials	very serious [f]	not serious [g]	not serious	not serious	none	At 2 years (the minimum duration of follow-up), patient satisfaction with anticoagulation, as measured by the DASS (in which scores range from 25 to 225, with lower scores indicating better satisfaction), was greater in the self-testing group than in the clinic-testing group (difference, −2.4 points; 95% CI, −3.9 to −1.0; P = 0.002), and a cumulative gain in health utilities according to the Health Utilities Index Mark 319 was noted in the self-testing group as compared with the clinic-testing group (difference, 0.155 points; 95% CI, 0.111 to 0.198; P<0.001). (Matchar 2010, RCT)				⊕⊕◯◯ LOW	CRITICAL
Time in Therapeutic INR Range (follow up: range 3 months to 57 months; assessed with: Linear interpolation; Scale from: 0 to 100)												
6 [2-6, 9, 11, 12]	randomised trials	very serious [b]	not serious	not serious	not serious	none	1813	1888 [h]	-	MD **5.37 % higher** (3.17 higher to 7.56 higher)	⊕⊕◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Median annual risk among 11 RCTs comparing LMWH/VKA with DOAC in patients requiring treatment for VTE.[13-23] This risk was observed in the original trial at 6 months and to obtain the annual risk, we assumed a linear increase over time and doubled the risk observed at 6 months. See also the ASH guideline on Treatment of VTE

b. Lack of patient/physician blinding in all RCTs, uncertainty about randomization process and outcome assessment blinding in most RCTs

c. Lower and upper bounds of the 95% CI for the anticipated absolute effect include important benefit and no effect

d. Lower and upper bounds of the 95% CI for the anticipated absolute effect include important benefit and harm

e. High bleeding risk of 2.1% in patients treated with anticoagulants for 6 months, from a systematic review of 13 prospective cohort studies and 56 randomized trials.[24] See also the ASH guideline on Treatment of VTE

f. Subjective outcome without blinding

g. Inconsistency cannot be determined as only one study reported quality of life

h. Based on mean TTR of non-PST groups in included RCTs

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Question #7

Should **point-of-care INR testing by the patient at home and self-adjustment of VKA dose (patient self-management; PSM)** vs. **any other management approach** be used in **patients receiving maintenance VKA therapy for treatment of VTE**?

POPULATION:	patients receiving maintenance VKA therapy for treatment of VTE
INTERVENTION:	point-of-care INR testing by the patient at home and self-adjustment of VKA dose (patient self-management; PSM)
COMPARISON:	any other management approach
MAIN OUTCOMES:	Mortality; Pulmonary Embolism - Moderate; Deep Venous Thrombosis in the Upper Leg - Moderate; Major Bleeding; Quality of Life; Time in Therapeutic INR Range;
SETTING:	Outpatient
PERSPECTIVE:	Clinical recommendation - Population perspective

BACKGROUND: Patients using a vitamin K antagonist for VTE treatment need to keep the International Normalized Ratio (INR) within the therapeutic range in order to achieve an optimal balance for the risk of VTE recurrence and bleeding. To achieve this the INR needs to be monitored in order to decide whether a dose change is needed. To monitor their INR patients have to go to a laboratory or clinical office on a regular basis, and they have to wait for the dosing advice from their healthcare provider based on the new INR result. Patient self-management (PSM) at home, which includes self-testing of the INR with a point-of-care device and making their own dosing decisions accordingly, could reduce patient inconvenience and by actively engaging the patient in their care PSM might improve clinical outcomes.

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies	Patients using a vitamin K antagonist for VTE treatment need to keep the International Normalized Ratio (INR) within the therapeutic range in order to achieve an optimal balance for the risk of VTE recurrence and bleeding. To achieve this the INR needs to be monitored in order to decide whether a dose change is needed. To monitor their INR patients have to go to a laboratory or clinical office on a regular basis, and they have to wait for	

	○ Don't know	the dosing advice from their healthcare provider based on the new INR result. Patient self-management (PSM) at home, which includes self-testing of the INR with a point-of-care device and making their own dosing decisions accordingly, could reduce patient inconvenience and by actively engaging the patient in their care PSM might improve clinical outcomes.	
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	For research evidence on Desirable and Undesirable anticipated effects, as well as the certainty of this evidence, see the **Evidence Profile** in the **Appendix**.	The panel considered the possibility that the effect of PSM could differ according to management in the comparator group (primary care vs. anticoagulation management service [AMS]). However, the effect of PSM on the desirable anticipated effects did not differ when comparing between the different comparator groups; AMS alone, primary care provider alone, or a mix of AMS and primary care).
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		The panel considered the possibility that the effect of PSM could differ according to management in the comparator group (primary care vs. anticoagulation management service [AMS]). However, the effect of PSM on the undesirable anticipated effects did not differ when comparing

			between the different comparator groups; AMS alone, primary care provider alone, or a mix of AMS and primary care).
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ● Low ○ Moderate ○ High ○ No included studies		Although TTR was of Very low certainty, the panel judged the overall certainty as Low as the more critical outcomes were rated Low, Moderate or High certainty.
VALUES	**Is there important uncertainty about or variability in 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	**Utility related information - the relative importance of outcomes** *Relative importance of the outcomes on a scale 0.00-1.00 with 1.00 indicating a patient comparing the outcome with being in 'Full health' and 0.00 comparing the outcome with being 'Dead'* <u>Our systematic review found that the relative importance of the outcomes is as follows:</u> - Pulmonary embolism: 0.63-0.93 (different methods)[1-3] - Deep vein thrombosis: 0.64-0.99 (different methods)[1-5] - Deep vein thrombosis patients' own current health: 0.95 (Time trade off)[3] - Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off)[1, 3]	

		- Muscular bleeding: 0.76 (time trade off)[3] - Minor intracranial bleeding event: 0.75 (standard gamble)[1] - Major intracranial bleeding event: 0.15 (standard gamble)[1] - Central nervous system bleeding: 0.29-0.60 (standard gamble)[6, 7] <u>Our survey among ASH guideline panel members found that the relative importance of QoL and TTR adherence is as follows:</u> - Quality of life (QoL) impairment: 0.57 [SD 0.23] (ASH panels utility rating) - Low time in therapeutic range (TTR): 0.74 [SD 0.25] (ASH panels utility rating)	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		Low quality evidence showed small desirable effects and trivial undesirable effects, with possibly important uncertainty or variability in how much people value the outcomes. There were no differences according to the specific care settings PSM was compared with.

RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**The following economic analyses were identified:** <u>Cost of patient self-testing</u> Overall mean healthcare costs in the PSM arm were significantly higher at £417 (CI £394–£442) compared with £122 (CI £103– £144) in the control arm.[8] <u>Cost of clinical events</u> Cost of PE (event cost): $11,616 [9] Cost of recurrent VTE (outpatient, hospitalization, and pharmacy cost in 1-year following VTE event): $11,120 [10] Cost of bleeding:[10] - 6 months following DVT: $11,018 for patients with major bleed - Per-event cost estimated over variable follow-up (mean follow-up = 21.3 months): $22,885 for bleed event requiring hospitalization - Per-event cost: base case treatment of bleeds = $9,935 <u>Cost of medication</u> - Warfarin, per month: $15.84 - $51.50 [11]	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ● Low ○ Moderate ○ High ○ No included studies		

COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	**The following cost-effectiveness analyses were identified:** Two reviews and one modeling study showed that PSM is likely to be cost-effective compared with usual care:[12-14] - The CADTH 2014 report showed that in the Canadian setting, PSM emerged as a cost-effective option at an incremental cost-effectiveness ratio of $13,028 CAD per QALY gained compared with laboratory testing. When considering the expanded health care-payer perspective (i.e., inclusive of patient travel costs for clinic and laboratory visits), PSM was the least costly option, dominating the other three strategies (i.e., PST, clinic-based POC and laboratory testing) [12] - The HQO 2009 report showed that in the Ontario setting PSM was the most cost-effective option when compared with PST, provider point-of-care testing and usual care [13] - Regier 2006 showed that in the Canadian setting the incremental cost-effectiveness ratio for PSM vs. physician care was $14,129 per QALY [14] However, one review and one RCT did not show PSM to be cost-effective:[8, 15] - The Connock 2007 review showed that in the UK setting PSM was more expensive than current routine care (£417 versus £122 per patient-year) and concluded that using a cost-effectiveness threshold of £30,000 per QALY gained, PSM does not appear to be cost-effective [15] - Jowett 2006 showed that in the UK setting the incremental cost-effectiveness ratio for PSM was £32,716 per QALY gained [8]	
EQUITY	**What would be the impact on health equity?** ● Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies	**No direct research evidence found for PSM, but indirect evidence for PST:** One observational study showed that successful home monitoring of prothrombin with a PST device required adequate levels of cognition and manual dexterity. Training a caregiver modestly increased the proportion of patients who can perform PST. [16]	PSM is labor intensive and the panel assumed that a small proportion of patients can do this.

	○ Don't know	One observational study showed that patients living farther away from the anticoagulation clinic did not benefit to a larger extent than patients living close to the clinic, and restricting access to patients living farther away is not likely to improve cost-effectiveness of PST. [17]	One panel member judged 'Probably reduced'.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	**Observational evidence from RCT populations showed the following acceptability among patients:** <u>Patients</u> Two RCTs showed that PSM improved treatment satisfaction and decreased daily hassles, psychological distress and strain on the social network. [18-20]	The panel judged that acceptability will vary a lot by patient and health system. Some patients may be scared of self-testing and making dosing decisions. Some patients would want to do PSM but would need comfort and support with the decision making and learn a lot about it.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**No direct research evidence found for PSM, but indirect observational evidence for PST showed the following acceptability and concerns among key stakeholders:** <u>Patients</u> Among patients who were offered or tried PST, most preferred point-of-care self-testing over laboratory testing. [21-25] <u>Healthcare providers</u> Providers are generally positive about PST. Concerns include unintended self-management and the need for quality assurance of the point-of-care device. [26]	The panel judged that intervention implementation will depend on the ability of the patients to perform self-testing and making dosing decisions.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies	

	JUDGEMENT							IMPLICATIONS
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies	
EQUITY	**Reduced**	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	Probably favors INR point-of-care testing by the patient at home and self-adjustment of VKA dose (PSM)

Should point-of-care INR testing by the patient at home and self-adjustment of VKA dose (patient self-management; PSM) vs. any other management approach be used in patients receiving maintenance VKA therapy for treatment of VTE?

Type of recommendation

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention

	○	○	○	○	●	

Conclusions

RECOMMENDATION	The ASH guideline panel recommends using point-of-care INR testing by the patient at home and self-adjustment of VKA dose (patient self-management; PSM) over any other management approach including patient self-testing in suitable patients (those with demonstrated competency to perform PSM and can afford this option) receiving maintenance VKA therapy for treatment of VTE (strong recommendation based on low certainty in the evidence).
JUSTIFICATION	This benefit is dependent upon patients and healthcare systems being able to afford and manage the self-testing equipment and patients being able to make independent decisions about VKA dosing based on INR result. The panel felt that PSM was superior to PST as it has shown reduction in mortality. Although the panel felt like a strong recommendation was warranted based on the available evidence, in settings where resources are limited or when patients are not willing or able to perform PSM, deviation from this recommendation is appropriate.
SUBGROUP CONSIDERATIONS	No subgroup considerations.
IMPLEMENTATION CONSIDERATIONS	Systems using PSM should be able to ensure quality assurance of the testing equipment and patient's ability to obtain accurate INR results and make rationale VKA dosing decisions. The panel considered that a potential benefit of alternative care options is that loss to follow up appears less likely compared to PSM as patients would have to return to clinics more frequently. The panel considered that lack of awareness of PSM by primary care providers is a potential barrier. The panel calls upon payers to carefully evaluate current reimbursement regulations and make changes as necessary to ensure that providers and patients are aware of this testing option, while also ensuring that unnecessary testing is not incentivized.
MONITORING AND EVALUATION	No monitoring and evaluation considerations.
RESEARCH PRIORITIES	The panel identified the following additional research questions: 1) What is the comparative effectiveness of PSM compared to other INR testing strategies specifically in patients with VTE?

	2) What is the comparative effectiveness of PSM compared to DOAC therapy? 3) What minimum competencies are required to engage in PSM and what is the most effective way to train patients to perform PSM?

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Appendix – Evidence Profile

Q7. In patients receiving maintenance VKA therapy for treatment of VTE should point-of-care INR testing by the patient at home and self-adjustment of VKA dose (patient self-management; PSM) vs. any other management approach be used?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**INR point-of-care testing by the patient at home and self-adjustment of VKA dose (PSM)**	**any other management approach**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality (follow up: range 3 months to 24 months)												
11 [1-24]	randomised trials	not serious	not serious	not serious	not serious	none	32/1824 (1.8%)	3.9% [a]	RR 0.58 (0.38 to 0.89)	**16 fewer per 1,000** (from 4 fewer to 24 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Pulmonary Embolism - Moderate (follow up: range 3 months to 24 months; assessed with: Thromboembolic events)												
14 [1-23, 25-30]	randomised trials	serious [b]	not serious	not serious	not serious	none	34/1989 (1.7%)	2.0% [a]	RR 0.48 (0.32 to 0.71)	**10 fewer per 1,000** (from 6 fewer to 14 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Deep Venous Thrombosis in the Upper Leg - Moderate (follow up: range 3 months to 24 months; assessed with: Thromboembolic events)												
14 [1-23, 25-30]	randomised trials	serious [b]	not serious	not serious	not serious	none	34/1989 (1.7%)	2.6% [a]	RR 0.48 (0.32 to 0.71)	**14 fewer per 1,000** (from 8 fewer to 18 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**INR point-of-care testing by the patient at home and self-adjustment of VKA dose (PSM)**	**any other management approach**	**Relative (95% CI)**	**Absolute (95% CI)**		
Major Bleeding (follow up: range 3 months to 24 months)												
15 [1-30]	randomised trials	serious [b]	not serious	not serious	not serious	none	75/2047 (3.7%)	1.7% [a,c]	RR 1.09 (0.80 to 1.50)	**2 more per 1,000** (from 3 fewer to 9 more)	⊕⊕⊕◯ MODERATE	CRITICAL
								2.1% [a,c]		**2 more per 1,000** (from 4 fewer to 11 more)		
Quality of Life (follow up: mean 4 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	INR point-of-care testing by the patient at home and self-adjustment of VKA dose (PSM)	any other management approach	Relative (95% CI)	Absolute (95% CI)		
2 [17, 18, 24, 30]	randomised trials	very serious [d]	not serious [e]	not serious	not serious	none	"General treatment satisfaction and daily hassles scores improved in the self-management group and remained unchanged in the routine care group. The scores of self-efficacy and distress improved in both groups, but improved significantly more in the self management group (Table 3). The general treatment satisfaction scores displayed the most pronounced improvement. The intervention had no significant effect on the strained social network scores." (Sawicki 1999, RCT) "Both groups were comparable with regard to quality of life topics at baseline (Table 2). After 4 months, treatment satisfaction significantly improved in the self management group compared with the control group (p<0.001). Daily hassles, psychological distress, and a strained social network all significantly decreased in the self-management group compared to the control group (p=0.024, p=0.029, and p<0.001, respectively). Self-efficacy increased in both groups (p<0.05), but the difference between the groups was not significant." (Verret 2012, RCT)				⨁⨁◯◯ LOW	CRITICAL
Time in Therapeutic INR Range (follow up: range 3 months to 24 months; Scale from: 0 to 100)												
9 [1-5, 13-16, 23, 24, 28-31]	randomised trials	very serious [f]	serious [g]	not serious	serious [h]	none	1166	1128 [i]	-	MD **4.41 % higher** (0.09 lower to 8.92 higher)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Median annual risk among 11 RCTs comparing LMWH/VKA with DOAC in patients requiring treatment for VTE.[32-42] This risk was observed in the original trial at 6 months and to obtain the annual risk, we assumed a linear increase over time and doubled the risk observed at 6 months. See also the ASH guideline on Treatment of VTE

b. Lack of patient/physician blinding in all, uncertainty about randomization process and outcome assessment in most

c. High bleeding risk of 2.1% in patients treated with anticoagulants for 6 months, from a systematic review of 13 prospective cohort studies and 56 randomized trials.[43] See also the ASH guideline on Treatment of VTE

d. Subjective outcome with lack of blinding

e. Inconsistency cannot be determined as only one study reported quality of life

f. Surrogate outcome with lack of patient/physician blinding in all, uncertainty about randomization process and outcome assessment in most

g. I2 = 85%; effect ranges from TTR improvement to worsening

h. Lower and upper bounds of the 95% CI for the anticipated absolute effect include important benefit and no effect

i. Based on mean TTR from non-PSM groups in included RCTs

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Question #9

Should **clinicians monitor anti-factor Xa level to guide LMWH dose adjustment** vs. **not use such monitoring** in **patients with renal dysfunction (creatinine clearance or GFR <30 mL/min) receiving LMWH therapy for treatment of VTE**?

POPULATION:	patients with renal dysfunction (creatinine clearance or GFR <30 mL/min) receiving LMWH therapy for treatment of VTE	**BACKGROUND:**	Given that LMWH is primarily cleared by the kidneys, patients with severe renal dysfunction receiving LMWH for treatment of VTE are at high risk of bleeding. It is unclear whether anti-factor Xa monitoring and subsequent dose adjustments lead to improved clinical outcomes among renal dysfunction patients, in comparison to no such monitoring.[1-3] Improper LMWH dosing in patients with renal impairment has been observed in practice, but is unclear if this is related to lack of monitoring.[4, 5]
INTERVENTION:	anti-factor Xa level monitoring to guide LMWH dose adjustment		
COMPARISON:	not use such monitoring		
MAIN OUTCOMES:	Mortality ; PE - Moderate severity; DVT in upper leg - Moderate severity; Major bleeding ; Quality of life impairment;		
SETTING:	Inpatient and outpatient		
PERSPECTIVE:	Clinical recommendation - Population perspective		

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Given that LMWH is primarily cleared by the kidneys, patients with severe renal dysfunction receiving LMWH for treatment of VTE are at high risk of bleeding. It is unclear whether anti-factor Xa monitoring and subsequent dose adjustments lead to improved clinical outcomes among renal dysfunction patients, in comparison to no such monitoring.[1-3] Improper LMWH dosing in patients with renal impairment has been observed in practice, but is unclear if this is related to lack of monitoring.[4, 5]	

DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	For research evidence on Desirable and Undesirable anticipated effects, as well as the certainty of this evidence, see the **Evidence Profile** in the **Appendix**.	Judgement based on the major bleeding rates from indirect comparison.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies		Very low certainty in evidence for effects due to very serious indirectness and serious imprecision.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability	**Utility related information - the relative importance of outcomes** *Relative importance of the outcomes on a scale 0.00-1.00 with 1.00 indicating a patient comparing the outcome with being in 'Full health' and 0.00 comparing the outcome with being 'Dead'*	

	○ No important uncertainty or variability	<u>Our systematic review found that the relative importance of the outcomes is as follows:</u> - Pulmonary embolism: 0.63-0.93 (different methods) [6-8] - Deep vein thrombosis: 0.64-0.99 (different methods) [6-10] - Deep vein thrombosis patients' own current health: 0.95 (Time trade off) [8] - Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) [6, 8] - Muscular bleeding: 0.76 (time trade off) [8] - Minor intracranial bleeding event: 0.75 (standard gamble) [6] - Major intracranial bleeding event: 0.15 (standard gamble) [6] - Central nervous system bleeding: 0.29-0.60 (standard gamble) [11, 12] <u>Our survey among ASH guideline panel members found that the relative importance of QoL and TTR adherence is as follows:</u> - Quality of life (QoL) impairment: 0.57 [SD 0.23] (ASH panels utility rating) - Low time in therapeutic range (TTR): 0.74 [SD 0.25] (ASH panels utility rating) <u>Two observational studies reported the following patient considerations regarding treatment burden and expectations:</u> For patients receiving low molecular weight heparin, patients placed high score on "importance of ease of use",	

		"expectations of symptom relief", and "confidence in the treatment to prevent blood clots" while they had low score of treatment-related side effects (bruise, bleeding). Lowest scores were reported on "worries about mistakes" and "worries about cost". [13, 14]	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know		Very low quality evidence showed moderate desirable effects in terms of a lower bleeding rate and trivial undesirable effects, with possibly important uncertainty or variability in how much people value the outcomes. Due to very serious indirectness and serious imprecision the panel considered the evidence to be of such low certainty that no judgement could be made for the balance of effects.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**The following economic analyses were identified:** <u>Cost of blood tests</u> The 2016 USD cost of the anti-Xa assay is: $37.53 For comparison: Prothrombin Time W/INR: $5.44 PTT (Partial Thromboplastin Time): $6.92 CBC with auto-differential: $11.59 <u>Cost of clinical events</u> Cost of PE (event cost): $11,616 [15] Cost of recurrent VTE (outpatient, hospitalization, and pharmacy cost in 1-year following VTE event): $11,120 [16]	If laboratory fails to ensure standardization and reproducibility of anti-Xa levels, dosing decisions could be based on irrelevant measures.

		Cost of bleeding [16] - 6 months following DVT: $11,018 for patients with major bleed - Per-event cost estimated over variable follow-up (mean follow-up = 21.3 months): $22,885 for bleed event requiring hospitalization - Per-event cost: base case treatment of bleeds = $9,935 <u>Cost of medication</u> - LMWH, per week: $199.92 - $712.00 [17]	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies		
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	The panel could not provide a judgement as health effects are uncertain and no cost-effectiveness analyses were identified.

EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified.	Anti-factor Xa level monitoring is most likely done in hospitalized patients.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	No research evidence identified.	Payers should not and would not pay for a test that is not useful. However, the fact that the test is done indicates that it may be acceptable.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The following barriers have been reported in observational studies: 1) Testing not widely available [18] 2) Poor standardization of testing [18] 3) Poor reproducibility of testing [19-21]	Laboratories are testing anti-factor Xa levels, but the lack of standardization and reproducibility makes a "proper" dose adjustment impossible. Nevertheless, testing and making any dose adjustment based on that is probably feasible.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know	
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**	
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies	

	JUDGEMENT							IMPLICATIONS
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**	
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Should clinicians monitor anti-factor Xa level to guide LMWH dose adjustment vs. not use such monitoring in patients with renal dysfunction (creatinine clearance or GFR <30 mL/min) receiving LMWH therapy for treatment of VTE?

Type of recommendation

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	●	○	○	○

Conclusions

RECOMMENDATION	The ASH guideline panel suggests against using anti-factor Xa level monitoring to guide LMWH dose adjustment in patients with renal dysfunction (creatinine clearance or GFR <30 mL/min) receiving treatment for VTE (conditional recommendation based on very low certainty in the evidence).
JUSTIFICATION	The guideline panel was unable to evaluate the net benefit associated with adjusting LMWH doses based the results of anti-factor Xa monitoring due to the limited body of available evidence. However, because of concerns relating to anti-factor Xa test standardization and reproducibility and lack of correlation between bleeding events and anti-factor Xa levels, the panel suggests against adjusting LMWH doses based on anti-factor Xa level monitoring. Seven panel members preferred making a strong recommendation against the intervention, but this majority was not sufficiently large (<80%) to satisfy the criterion for a strong recommendation (7 voted for Strong, 5 voted for Conditional).
SUBGROUP CONSIDERATIONS	No subgroup considerations.
IMPLEMENTATION CONSIDERATIONS	No implementation considerations.
MONITORING AND EVALUATION	No monitoring and evaluation considerations.
RESEARCH PRIORITIES	The panel identified the following additional research questions: 1) What are the anti-factor Xa level cut-offs (performed in a manner that ensures accuracy and reproducibility) that correlate with risk of recurrent VTE and bleeding events? 2) What percentage change in LMWH dose in response to an out-of-range anti-factor Xa level is optimal to return the level to the therapeutic range? 3) What is the comparative effectiveness of adjusting LMWH doses based on the results of anti-factor Xa levels (performed in a manner that ensures accuracy and reproducibility) vs. no such monitoring in a patients with estimated creatinine clearance <30 mL/min requiring treatment for VTE?

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Appendix – Evidence Profile

Q9. In patients with renal dysfunction (creatinine clearance or GFR <30 mL/min) receiving LMWH therapy for treatment of VTE should clinicians monitor anti-factor Xa level to guide LMWH dose adjustment versus no such monitoring?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH dose adjustment be based on anti-factor Xa level monitoring**	**no such monitoring**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality (follow up: 90 days; assessed with: All-cause mortality, but PE as cause of death could not be ruled out)												
1 [1]	observational studies [a]	not serious [b]	not serious [c]	very serious [d]	not serious	none	4/70 (5.7%)	[e]	not estimable		⨁◯◯◯ VERY LOW	CRITICAL
PE - Moderate severity - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
DVT in upper leg - Moderate severity (follow up: 90 days; assessed with: Recurrent VTE confirmed objectively through diagnostic imaging)												
1 [1]	observational studies [a]	not serious [b]	not serious [c]	very serious [d]	not serious	none	2/70 (2.9%)	[e]	not estimable		⨁◯◯◯ VERY LOW	CRITICAL
Major bleeding (follow up: range 5 days to 90 days; assessed with: as defined by individual studies following therapeutic dose of enoxaparin)[f]												
9 [1-9]	observational studies	very serious [g]	not serious	serious [h]	serious [i]	none	6/239 (2.5%)	7/65 (10.8%) [j]	RR 0.23 (0.08 to 0.67) [k]	**83 fewer per 1,000** (from 36 fewer to 99 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life impairment - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

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

Explanations

a. Data was abstracted from the tinzaparin arm of the IRIS RCT (Leizorowicz 2011), which compared tinzaparin to UFH for the treatment of acute VTE.

b. Risk of bias cannot be assessed because the study did not report a comparison.

c. Inconsistency cannot be determined as no studies reported the direct comparison of intervention vs. control.

d. The study did not report a direct comparison, but only the event rate for the intervention group.

e. Baseline risk was not found for patients with renal dysfunction on LWMH without anti-Xa monitoring.

f. Combined studies administered different LMWHs (enoxaparin, tinzaparin) and utilized different dosing regimens (once daily, twice daily).

g. Very high risk of confounding as the event rate for the intervention group [1-8] came from different studies than the event rate for the control group [9]. No adjustment for important differences in study designs, populations and outcome assessment.

h. Studies included not only patients with acute VTE, but also acute coronary syndromes and atrial fibrillation.

i. Lower and upper bounds of the 95% CI for the anticipated absolute effect include highly important benefit and somewhat important benefit

j. The risk of major bleeding with no anti-Xa monitoring, as reported in Thorevska (2004). The study did not monitor anti-Xa levels for renal dysfunction patients receiving fixed doses of enoxaparin (1 mg/kg body weight administered subcutaneously twice a day).

k. Comparison based on the pooled event rate for the intervention group and a single study control group. The weighted pooled event rate for the intervention group was calculated by transforming all study event rates using the Freeman-Tukey arcsine transformation, calculating a pooled estimate of the transformed event rates, and back transforming this pooled estimate to a pooled event rate. (Freeman-Tukey 1950). The weighted pooled event rate for the intervention group was 2.7% (95% CI: 0.9-5.2%), which is similar to the overall unweighted event rate of 2.5% (6/239). Therefore, the unweighted event rate of 2.5% was used to calculate the relative effect and anticipated absolute effect.

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Question #10

Should **clinicians monitor anti-factor Xa level to guide LMWH dose adjustment** vs. **not use such monitoring** in **patients with obesity receiving LMWH therapy for treatment of VTE**?

POPULATION:	patients with obesity receiving LMWH therapy for treatment of VTE
INTERVENTION:	anti-factor Xa level monitoring to guide LMWH dose adjustment
COMPARISON:	not use such monitoring
MAIN OUTCOMES:	Mortality; PE - Moderate severity ; DVT in upper leg - Moderate severity; Major bleeding ; Quality of life impairment;
SETTING:	Inpatient and outpatient
PERSPECTIVE:	Clinical recommendation - Population perspective

BACKGROUND: Clinicians use weight-based dosing strategies for patients receiving LMWH for treatment of VTE. Uncertainty remains with respect to the optimal dosing strategy for obese patients with VTE, as there is concern that dosing based on actual body weight may increase risk of bleeding. It is unclear whether antifactor-Xa monitoring and subsequent dose adjustments improve clinical outcomes for obese patients, in comparison to no such monitoring.[1-3] Improper LMWH dosing in obese patients has been observed in clinical practice.[4]

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Clinicians use weight-based dosing strategies for patients receiving LMWH for treatment of VTE. Uncertainty remains with respect to the optimal dosing strategy for obese patients with VTE, as there is concern that dosing based on actual body weight may increase risk of bleeding. It is unclear whether antifactor-Xa monitoring and subsequent dose adjustments improve clinical outcomes for obese patients, in comparison to no such monitoring.[1-3] Improper LMWH dosing in obese patients has been observed in clinical practice.[4]	

DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	For research evidence on Desirable and Undesirable anticipated effects, as well as the certainty of this evidence, see the **Evidence Profile** in the **Appendix**.	Evidence for all outcomes points to no benefit.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know		Judgement based on 3% increased risk for major bleeding and approximately 0.2% increased risk for VTE. Included studies only addressed monitoring during hospitalization.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies		Very low certainty in evidence for effects due to very serious indirectness and serious imprecision.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability	**Utility related information - the relative importance of outcomes** *Relative importance of the outcomes on a scale 0.00-1.00 with 1.00 indicating a patient comparing the outcome with being in 'Full health' and 0.00 comparing the outcome with being 'Dead'*	

	○ No important uncertainty or variability	<u>Our systematic review found that the relative importance of the outcomes is as follows:</u> - Pulmonary embolism: 0.63-0.93 (different methods) [5-7] - Deep vein thrombosis: 0.64-0.99 (different methods) [5-9] - Deep vein thrombosis patients' own current health: 0.95 (Time trade off) [7] - Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) [5, 7] - Muscular bleeding: 0.76 (time trade off) [7] - Minor intracranial bleeding event: 0.75 (standard gamble) [5] - Major intracranial bleeding event: 0.15 (standard gamble) [5] - Central nervous system bleeding: 0.29-0.60 (standard gamble) [10, 11] <u>Our survey among ASH guideline panel members found that the relative importance of QoL and TTR adherence is as follows:</u> - Quality of life (QoL) impairment: 0.57 [SD 0.23] (ASH panels utility rating) - Low time in therapeutic range (TTR): 0.74 [SD 0.25] (ASH panels utility rating) <u>Two observational studies reported the following patient considerations regarding treatment burden and expectations:</u> For patients receiving low molecular weight heparin, patients placed high score on "importance of ease of use", "expectations of symptom relief", and "confidence in the treatment to prevent blood clots" while they had low score of treatment-related side effects (bruise, bleeding). Lowest scores were reported on "worries about mistakes" and "worries about cost". [12, 13]	

BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		Very low quality evidence showed trivial desirable effects and moderate undesirable effects in terms of increased risk for major bleeding, with possibly important uncertainty or variability in how much people value the outcomes.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**The following economic analyses were identified:** <u>Cost of blood tests</u> The current 2016 USD cost of the anti-Xa assay is: $37.53 For comparison: Prothrombin Time W/INR: $5.44 PTT (Partial Thromboplastin Time): $6.92 CBC with auto-differential: $11.59 <u>Cost of clinical events</u> Cost of PE (event cost): $11,616 [14] Cost of recurrent VTE (outpatient, hospitalization, and pharmacy cost in 1-year following VTE event): $11,120 [15] Cost of bleeding: [15] - 6 months following DVT: $11,018 for patients with major bleed - Per-event cost estimated over variable follow-up (mean follow-up = 21.3 months): $22,885 for bleed event requiring hospitalization - Per-event cost: base case treatment of bleeds = $9,935 <u>Cost of medication</u> - LMWH, per week: $199.92 - $712.00 [16]	

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies		
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	The panel could not provide a judgement as no cost-effectiveness analyses were identified.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified.	Anti-factor Xa level monitoring is most likely done in hospitalized patients.

ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	No research evidence identified.	Payers should not and would not pay for a test that is not useful. However, the fact that the test is done indicates that it may be acceptable.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The following barriers have been reported by observational studies: 1) Not widely available [17] 2) Poor standardization [17] 3) Poor reproducibility [18-20]	Laboratories are testing anti-factor Xa levels, but the lack of standardization and reproducibility makes a "proper" dose adjustment impossible. Nevertheless, testing and making any dose adjustment based on testing results is probably feasible.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know	

	JUDGEMENT							IMPLICATIONS
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**	
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	

	JUDGEMENT							IMPLICATIONS
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Should clinicians monitor anti-factor Xa level to guide LMWH dose adjustment vs. not use such monitoring in patients with obesity receiving LMWH therapy for treatment of VTE?

Type of recommendation

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	●	○	○	○	○

Conclusions

RECOMMENDATION	The ASH guideline panel recommends against using anti-factor Xa level monitoring to guide LMWH dose adjustment in patients with obesity receiving for treatment of VTE (strong recommendation based on very low certainty in the evidence).
JUSTIFICATION	The guideline panel determined that there is very low certainty evidence for net harm from adjusting LMWH doses based on anti-factor Xa level monitoring over no such monitoring in patients with obesity on LMWH therapy for treatment of VTE. Despite the very low certainty evidence 10 panelists felt that a strong recommendation was warranted due to concerns relating to anti-factor Xa test standardization and reproducibility, lack of correlation between bleeding events and anti-factor Xa levels, and no biologic

	evidence that anti-factor Xa testing is needed in patients with obesity. The 10 out of 12 panelists voting in favor of a strong recommendation satisfied the criterion to make a strong recommendation against the intervention (80% or more).
SUBGROUP CONSIDERATIONS	No subgroup considerations.
IMPLEMENTATION CONSIDERATIONS	No implementation considerations.
MONITORING AND EVALUATION	No monitoring and evaluation considerations.
RESEARCH PRIORITIES	The panel identified the following additional research questions: 1) What are the anti-factor Xa level cut-offs (performed in a manner that ensures accuracy and reproducibility) that correlate with risk of recurrent VTE and bleeding events? 2) What percentage change in LMWH dose in response to an out-of-range anti-factor Xa level is optimal to return the level to the therapeutic range? 3) What is the comparative effectiveness of adjusting LMWH doses based on the results of anti-factor Xa levels (performed in a manner that ensures accuracy and reproducibility) vs. no such monitoring in a patients with obesity requiring treatment for VTE?

References for Evidence to Decision (EtD) table

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Appendix – Evidence Profile

Q10. In patients with obesity receiving LMWH therapy for treatment of VTE should clinicians monitor anti-factor Xa level to guide LMWH dose adjustment versus no such monitoring?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH dose adjustment be based on anti-factor Xa level monitoring**	**no such monitoring**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
PE - Moderate severity (assessed with: diagnostic evidence and physician documentation during course of hospitalization)												
4 [1-4]	observational studies	very serious [a]	not serious	serious [b]	serious [c]	none	1/63 (1.6%) [d]	1/193 (0.5%) [e]	RR 6.13 (0.57 to 66.44) [f]	**27 more per 1,000** (from 2 fewer to 339 more)	⨁◯◯◯ VERY LOW	CRITICAL
DVT in upper leg - Moderate severity (assessed with: diagnostic evidence and physician documentation during course of hospitalization)												
4 [1-4]	observational studies	very serious [a]	not serious	serious [b]	serious [c]	none	1/63 (1.6%) [d]	2/193 (1.0%) [e]	RR 3.06 (0.44 to 21.30) [f]	**21 more per 1,000** (from 6 fewer to 210 more)	⨁◯◯◯ VERY LOW	CRITICAL
Major bleeding (assessed with: as defined by individual studies)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**LMWH dose adjustment be based on anti-factor Xa level monitoring**	**no such monitoring**	**Relative (95% CI)**	**Absolute (95% CI)**		
5 [1-5]	observational studies	very serious [g]	serious [h]	very serious [b,i]	serious [j]	none	4/74 (5.4%)	2/193 (1.0%) [e]	RR 5.22 (0.98 to 27.88) [k]	**44 more per 1,000** (from 0 fewer to 279 more)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life impairment - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

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

Explanations

a. Very high risk of confounding as the event rate for the intervention group [2-4] came from different studies than the event rate for the control group [1]. No adjustment for important differences in study designs, populations and outcome assessment.

b. Definition of obesity varied among included studies.

c. Lower and upper bounds of the 95% CI for the anticipated absolute effect include important benefit and important harm.

d. One patient presented with both chronic-appearing pulmonary emboli and lower-extremity DVT.

e. The risk of major bleeding, PE and DVT (90-day follow-up) with no anti-Xa monitoring, as reported in Al-Yaseen (2005). [1] The study did not monitor anti-factor Xa levels for obese patients (body weight>90 kg) receiving fixed doses of dalteparin (mean daily dose=191 units/kg).

f. Comparison based on the pooled event rate for the intervention group and a single study control group. The weighted pooled event rate for the intervention group was calculated by transforming all study event rates using the Freeman-Tukey arcsine transformation, calculating a pooled estimate of the transformed event rates, and back transforming this pooled estimate to a pooled event rate. (Freeman-Tukey 1950). The weighted pooled event rate for the intervention group was 2.4% (95% CI: 0.1-7.6%), which is different from the overall unweighted event rate of 1.6% (1/63). Therefore, the weighted event rate of 2.4% was used to calculate the relative effect and anticipated absolute effect.

g. Very high risk of confounding as the event rate for the intervention group [2-5] came from different studies than the event rate for the control group [1]. No adjustment for important differences in study designs, populations and outcome assessment.

h. Combined studies administered different LMWHs (enoxaparin, tinzaparin) and utilized different dosing regimens (once daily, twice daily).

i. Participants in the included studies consisted of acute VTE, acute coronary syndrome, and atrial fibrillation patients.

j. Lower and upper bounds of the 95% CI for the anticipated absolute effect include important benefit and no effect.

k. Comparison based on the pooled event rate for the intervention group and a single study control group. The weighted pooled event rate for the intervention group was calculated by transforming all study event rates using the Freeman-Tukey arcsine transformation, calculating a pooled estimate of the transformed event rates, and back transforming this pooled estimate to a pooled event rate. (Freeman-Tukey 1950). The weighted pooled event rate for the intervention group was 5.0% (95% CI: 0.06-20.5%), which is similar to the overall unweighted event rate of 5.4% (4/74). Therefore, the unweighted event rate of 5.4% was used to calculate the relative effect and anticipated absolute effect.

References – Included Studies

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Question #11 – Good Practice Statement

Should renal function be monitored every 6-12 months vs. no such monitoring in patients with creatinine clearance ≥50 mL/min receiving DOAC therapy for treatment of VTE?

Good Practice Statement

In patients with creatinine clearance ≥50 mL/min receiving DOAC therapy for treatment of VTE, the ASH guideline panel believes that good practice includes renal function monitoring every 6-12 months (ungraded good practice statement).

Appendix – Support for Good Practice Statement criteria [1]

(i) Is the statement clear and actionable? Questions particular to good practice statements

Yes:

- Statement provides clear specification of procedure and timeframe

(ii) Is the message really necessary in regard to actual health care practice?

Yes:

- Most DOACs are at least partly cleared by the kidneys and renal function needs to be measured before starting treatment
- Worsening renal function (WRF) is common among patients on DOAC:
    - ROCKET AF – Rivaroxaban [2]: 26.3% among all study patients
        - WRF: >20% decrease in CrCl at any point during the study
        - Monitoring frequency: at 24 weeks and 52 weeks after randomization, at study end or early drug discontinuation, and further according to standard care
    - ARISTOTLE – Apixaban [3]: 13.6% during 12 months among all study patients
        - WRF: >20% annual decrease in eGFR
        - Monitoring frequency: every 3 months
    - Retrospective study with mix of DOACs [4]: 6.9% during 382 days among study patients with baseline eCCr ≥50 ml/min
        - WRF: eCCr <50 ml/min
        - Monitoring frequency: every few months

- Worsening renal function in patients using DOAC was associated with a higher risk of adverse events compared with patients who had stable renal function, specifically:
    - ROCKET AF – Rivaroxaban [2]: patients with WRF had a higher risk of vascular death
    - ARISTOTLE – Apixaban [3]: patients with WRF had a higher risk of stroke/SE, major bleeding and death
    - Retrospective study with mix of DOACs [4]: patients with WRF had a higher risk of major bleeding

(iii) After consideration of all relevant outcomes and potential downstream consequences, will implementing the good practice statement result in large net positive consequences?

Yes:

- Patients with diminished renal function often required a lower DOAC dose to balance optimal benefit and risk in RCTs
- Detecting worsening renal function will allow taking action according to what was part of the treatment protocols in RCTs. Based on RCT results, the panel expects that the risk of bleeding will be lowered as compared with not making treatment changes in case of undetected worsening renal function

(iv) Is collecting and summarizing the evidence a poor use of a guideline panel's limited time and energy (opportunity cost is large)?

Yes:

- The panel discussed the absence of direct evidence addressing this question, and decided that a good practice statement is most appropriate, which also saved time to address other guideline questions

(v) Is there a well-documented clear and explicit rationale connecting the indirect evidence?

Yes:

- Yes, see above

References

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Question #13

Should **resumption of oral anticoagulation therapy** vs. **discontinuation of oral anticoagulation therapy** be used in **patients receiving treatment for VTE who survive an episode of anticoagulation therapy related major bleeding**?

POPULATION:	patients receiving treatment for VTE who survive an episode of anticoagulation therapy related major bleeding
INTERVENTION:	resumption of oral anticoagulation therapy
COMPARISON:	discontinuation of oral anticoagulation therapy
MAIN OUTCOMES:	Mortality; Deep vein thrombosis in upper leg - Moderate severity; Pulmonary embolism - Moderate severity; Major bleeding; Quality of Life Impairment; Venous thromboembolism; Thromboembolism;
SETTING:	Inpatient
PERSPECTIVE:	Clinical considerations - population perspective

BACKGROUND: Once patients have survived a major bleeding episode on oral anticoagulation they are often considered to be at high risk for a recurrence of bleeding. As VTE risk and bleeding risk always need to be traded off when deciding to use oral anticoagulation, physicians might now be more hesitant to resume oral anticoagulation after the major bleeding. Therefore it is an important clinical issue to determine if resumption leads to better outcomes than no resumption.

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Once patients have survived a major bleeding episode on oral anticoagulation they are often considered to be at high risk for a recurrence of bleeding. As VTE risk and bleeding risk always need to be traded off when deciding to use oral anticoagulation, physicians might now be more hesitant to resume oral anticoagulation after the major bleeding. Therefore it is an important clinical issue to determine if resumption leads to better outcomes than no resumption.	

DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	For research evidence on Desirable and Undesirable anticipated effects, as well as the certainty of this evidence, see the **Evidence Profile** in the **Appendix**.	The panel judged that the intervention was associated with a moderate reduction in the risk for mortality and thromboembolism.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know		The panel judged that the intervention was associated with a moderate increase in the risk for major bleeding.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies		The panel judged that the evidence was of very low certainty primarily due to serious risk of bias and indirectness.
VALUES	**Is there important uncertainty about or variability in 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	**Utility related information - the relative importance of outcomes** *Relative importance of the outcomes on a scale 0.00-1.00 with 1.00 indicating a patient comparing the outcome with being in 'Full health' and 0.00 comparing the outcome with being 'Dead'*	

		<u>Our systematic review found that the relative importance of the outcomes is as follows:</u> - Pulmonary embolism: 0.63-0.93 (different methods) [1-3] - Deep vein thrombosis: 0.64-0.99 (different methods) [1-5] - Deep vein thrombosis patients' own current health: 0.95 (Time trade off) [3] - Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) [1, 3] - Muscular bleeding: 0.76 (time trade off) [3] - Minor intracranial bleeding event: 0.75 (standard gamble) [1] - Major intracranial bleeding event: 0.15 (standard gamble) [1] - Central nervous system bleeding: 0.29-0.60 (standard gamble) [4, 6] <u>Our survey among ASH guideline panel members found that the relative importance of QoL and TTR adherence is as follows:</u> - Quality of life (QoL) impairment: 0.57 [SD 0.23] (ASH panels utility rating) - Low time in therapeutic range (TTR): 0.74 [SD 0.25] (ASH panels utility rating)	

BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		The panel considered the balance between the reduced thromboembolism risk and increased major bleeding risk. 3.8 % bleeding increases, 0.8 to 2.1% VTE reduction, and reduced mortality that is questionable given residual confounding in the observational studies. The potential to avoid mortality was judged more important than increasing the risk of recurrent bleeding. The panel considered the evidence for resuming anticoagulation within 90 days.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**The following economic analyses were identified:** <u>Cost of hospitalization</u> In patients with atrial fibrillation (indirect evidence) who have had a warfarin-related intracerebral hemorrhage, therapy resumption reduced the mean 3-year hospitalization cost of hospitalized patients significantly by US $1,588 (95% confidence interval, −2,925 to −251) and was significantly correlated with fewer hospitalization days per hospitalized patient (−4.6 [95% confidence interval, −7.6 to −1.6]). [7] <u>Cost of clinical events</u> Cost of PE (event cost): $11,616 [8] Cost of recurrent VTE (outpatient, hospitalization, and pharmacy cost in 1-year following VTE event): $11,120 [9] Cost of bleeding: [9]	The panel considered costs associated with resuming anticoagulation therapy include the cost of medications and monitoring. There would be costs associated with bleeding events, but also savings associated with reduction in VTE events.

		- 6 months following DVT: $11,018 for patients with major bleed - Per-event cost estimated over variable follow-up (mean follow-up = 21.3 months): $22,885 for bleed event requiring hospitalization - Per-event cost: base case treatment of bleeds = $9,935 <u>Cost of medication</u> - Warfarin, per month: $15.84 - $51.50 [10] - DOAC, per month: $300.42 - $600.88 [10]	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ● Low ○ Moderate ○ High ○ No included studies		
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	The panel could not provide a judgment due to a lack of cost-effectiveness studies.

EQUITY	**What would be the impact on health equity?** ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified.	The panel considered that patients who are subject to barriers for using anticoagulation would now be at increased risk of not receiving appropriate anticoagulation.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	**Providers** One observational showed that anticoagulation prescribing in atrial fibrillation patients is substantially reduced immediately following physician exposure to a bleeding event. (indirect evidence) [11] One survey showed that neurosurgeons and neurologists usually resume anticoagulation in atrial fibrillation patients who had an intracranial hemorrhage with three-quarters resuming anticoagulation within 8-28 days. (indirect evidence) [12]	The patient representative panel members expressed that they find oral anticoagulation resumption acceptable. The panel also considered that providers might be concerned about causing further harm.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence identified.	The panel judged that the intervention is feasible as it is currently being used in practice.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies	

	JUDGEMENT							IMPLICATIONS
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**	
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know	

Should resumption of oral anticoagulation therapy vs. discontinuation of oral anticoagulation therapy be used in patients receiving treatment for VTE who survive an episode of anticoagulation therapy related major bleeding?

Type of recommendation

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○

Conclusions

RECOMMENDATION	The ASH guideline panel suggests resumption of oral anticoagulation therapy within 90 days rather than discontinuation of oral anticoagulation therapy in patients receiving treatment for VTE who survive an episode of oral anticoagulation therapy related major bleeding and who are at moderate to high risk for recurrent VTE and not at high risk for recurrent bleeding (conditional recommendation based on very low certainty in the evidence).
JUSTIFICATION	The guideline panel determined that there is probably a net health benefit from resuming anticoagulation therapy after surviving a major bleeding episode based on very low certainty evidence. Based on the body of available evidence, it is likely that anticoagulation therapy resumption reduces overall mortality and possibly also the development of thromboembolism, but also increases the risk of recurrent bleeding. Although some panel members felt that the impact on all-cause mortality was questionable and likely subject to confounding, the potential to avoid mortality was more important than increasing the risk of recurrent bleeding.
SUBGROUP CONSIDERATIONS	This recommendation specifically applies to patients who require long term or indefinite anticoagulation (i.e., are at moderate to high risk for recurrent VTE, are not at high risk for recurrent bleeding, and who are willing to continue anticoagulation therapy).
IMPLEMENTATION CONSIDERATIONS	The available evidence was insufficient to allow the panel to state with certainty the optimal timing of anticoagulation therapy resumption. However, the panel felt that waiting at least 2 weeks but not more than 90 days after the bleeding event is reasonable. Earlier resumption should be considered if the source of bleeding is identified and corrected.
MONITORING AND EVALUATION	No monitoring and evaluation considerations.
RESEARCH PRIORITIES	The panel identified the following additional research questions: 1) What is the optimal timing of and what patient-specific factors should influence anticoagulation therapy resumption? 2) As DOAC therapy has been associated with lower risk for major bleeding (particularly ICH), should patients who developed major bleeding during VKA therapy resume anticoagulation with a DOAC? 3) What is the impact on mortality, recurrent VTE and recurrent bleeding risk associated with resumption of anticoagulation therapy following extracranial bleeding from sites other than the gastrointestinal tract? 4) Is resuming anticoagulation therapy following major bleeding a cost-effective strategy?

References for Evidence to Decision (EtD) table

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Appendix – Evidence Profile

Q13. In patients receiving treatment for VTE who survive an episode of anticoagulation therapy related major bleeding should resumption of oral anticoagulation therapy vs. discontinuation of oral anticoagulation therapy be used?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**resumption of oral anticoagulation therapy**	**discontinuation of oral anticoagulation therapy**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality (follow up: range 3 months to 8 years)												
9 [1-9]	observational studies	serious [a]	serious [b]	serious [c]	not serious	none	409/2113 (19.4%)	845/2455 (34.4%) [d]	RR 0.59 (0.45 to 0.77)	**141 fewer per 1,000** (from 79 fewer to 189 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
								20.0% [d]		**82 fewer per 1,000** (from 46 fewer to 110 fewer)		
Deep vein thrombosis in upper leg - Moderate severity (follow up: range 3 months to 10 years; assessed with: DVT)												
7 [2, 7, 8, 10-13]	observational studies	serious [a]	not serious	serious [c]	serious [e]	none	8/532 (1.5%)	11/464 (2.4%)	RR 0.66 (0.25 to 1.75)	**8 fewer per 1,000** (from 18 fewer to 18 more)	⊕◯◯◯ VERY LOW	CRITICAL
Pulmonary embolism - Moderate severity (follow up: range 3 months to 10 years; assessed with: PE)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**resumption of oral anticoagulation therapy**	**discontinuation of oral anticoagulation therapy**	**Relative (95% CI)**	**Absolute (95% CI)**		
6 [1, 7, 8, 11-13]	observational studies	serious [a]	not serious	serious [c]	not serious	none	1/508 (0.2%)	12/425 (2.8%)	RR 0.26 (0.08 to 0.82)	**21 fewer per 1,000** (from 5 fewer to 26 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Major bleeding (follow up: range 3 months to 10 years)												
17 [1-17]	observational studies	serious [a]	not serious	serious [c]	not serious	none	299/2579 (11.6%)	230/3304 (7.0%)	RR 1.54 (1.18 to 2.02)	**38 more per 1,000** (from 13 more to 71 more)	⊕◯◯◯ VERY LOW	CRITICAL
Quality of Life Impairment - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

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

Explanations

a. In most studies, it was unclear when OAC was resumed, if OAC therapy changed during follow-up and if events occurred before or after OAC resumption

b. Non-overlapping confidence intervals, and I2 = 82%

c. The majority of studies included a mixed populations with a minority (<30%) of patients having VTE as the indication for long-term OAC therapy, and three studies only had patients with non-VTE patients (Qureshi 2014, Hernandez 2017, Nielsen 2017)

d. The median 90 day mortality among included studies was 20%

e. Lower and upper bounds of the 95% CI for the anticipated absolute effect include important benefit and important harm

References – Included studies

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Question #14

Should **temporary cessation of VKA plus administration of vitamin K** vs. **temporary cessation of VKA alone** be used in **patients receiving VKA for treatment of VTE with INR >4.5 but <10 and without clinically relevant bleeding**?

POPULATION:	patients receiving VKA for treatment of VTE with INR >4.5 but <10 and without clinically relevant bleeding
INTERVENTION:	temporary cessation of VKA plus administration of vitamin K
COMPARISON:	temporary cessation of VKA alone
MAIN OUTCOMES:	Mortality; Major bleeding; PE – Moderate severity; DVT in the upper leg — Moderate severity; Quality of Life Impairment; Emergency room visit; Hospitalization; Thromboembolism ; Proportion who reached goal INR;
SETTING:	Inpatient or outpatient
PERSPECTIVE:	Clinical recommendation - Population perspective

BACKGROUND: Patients on a vitamin K antagonist with an INR value well above the therapeutic range are at increased risk of bleeding. If the INR is >4.5 vitamin K antagonist treatment is temporarily stopped to lower the INR. In addition, administering vitamin K might shorten the time to INR normalization and prevent bleedings, but might also lower the INR too much and put patients at increased risk of VTE.

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Patients on a vitamin K antagonist with an INR value well above the therapeutic range are at increased risk of bleeding. If the INR is >4.5 vitamin K antagonist treatment is temporarily stopped to lower the INR. In addition, administering vitamin K might shorten the time to INR normalization and prevent bleedings, but might also lower the INR too much and put patients at increased risk of VTE.	

DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	For research evidence on Desirable and Undesirable anticipated effects, as well as the certainty of this evidence, see the **Evidence Profile** in the **Appendix**.	The desirable effects included rapid return to therapeutic INR range.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know		
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ● Low ○ Moderate ○ High ○ No included studies		Low certainty primarily due to serious imprecision for critical outcomes.
VALUES	**Is there important uncertainty about or variability in 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	**Utility related information - the relative importance of outcomes** *Relative importance of the outcomes on a scale 0.00-1.00 with 1.00 indicating a patient comparing the outcome with being in 'Full health' and 0.00 comparing the outcome with being 'Dead'*	

		<u>Our systematic review found that the relative importance of the outcomes is as follows:</u> - Pulmonary embolism: 0.63-0.93 (different methods) [1-3] - Deep vein thrombosis: 0.64-0.99 (different methods) [1-5] - Deep vein thrombosis patients' own current health: 0.95 (Time trade off) [3] - Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) [1, 3] - Muscular bleeding: 0.76 (time trade off) [3] - Minor intracranial bleeding event: 0.75 (standard gamble) [1] - Major intracranial bleeding event: 0.15 (standard gamble) [1] - Central nervous system bleeding: 0.29-0.60 (standard gamble) [6, 7] <u>Our survey among ASH guideline panel members found that the relative importance of QoL and TTR adherence is as follows:</u> - Quality of life (QoL) impairment: 0.57 [SD 0.23] (ASH panels utility rating) - ER visit: 0.75 [SD 0.26] (ASH panels utility rating) - Hospitalization: 0.71 [SD 0.27] (ASH panels utility rating)	

BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		Based on the low certainty evidence, the guideline panel was unable to determine whether there was net benefit or harm associated with administration of oral vitamin K in addition to withholding VKA doses for patients presenting with INRs between 4.5 and 10.0
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**The following economic analyses were identified:** <u>Cost of vitamin K</u> Cost of 1 tablet of vitamin K 5mg (mephytone): $66 [8] <u>Cost of clinical events</u> Cost of PE (event cost): $11,616 [9] Cost of recurrent VTE (outpatient, hospitalization, and pharmacy cost in 1-year following VTE event): $11,120 [10] Cost of bleeding: [10] - 6 months following DVT: $11,018 for patients with major bleed - Per-event cost estimated over variable follow-up (mean follow-up = 21.3 months): $22,885 for bleed event requiring hospitalization - Per-event cost: base case treatment of bleeds = $9,935	The panel felt that resource requirements associated with administering oral vitamin K are likely to be moderate owing to the high cost of pharmaceutical grade phytonadione (vitamin K) in the US. Other resource requirements include the need for some patients to make an additional trip to a pharmacy to acquire vitamin K prescriptions.

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ● Low ○ Moderate ○ High ○ No included studies		
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	There were no available studies assessing the cost-effectiveness associated with oral vitamin K administration.
EQUITY	**What would be the impact on health equity?** ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified.	The judgement was based on the cost of, and access to prescription vitamin K.

ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence identified.	The panel judged that vitamin K in oral or solution form would be acceptable for all stakeholders.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	One meta-analysis of RCTs reported the following facilitator and barrier for using vitamin K for elevated INR: 1) Vitamin K tablets as well as oral solutions can be used as they are equally effective. [11] 2) Quality and actual active ingredient content of available over-the-counter vitamin K formulations is variable. [12]	

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know	

	JUDGEMENT							IMPLICATIONS
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**	
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know	

	JUDGEMENT							IMPLICATIONS
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Should temporary cessation of VKA plus administration of vitamin K vs. temporary cessation of VKA alone be used in patients receiving VKA for treatment of VTE with INR >4.5 but <10 and without clinically relevant bleeding?

Type of recommendation

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	●	○	○	○

Conclusions

RECOMMENDATION	The ASH guideline panel suggests not using vitamin K in addition to temporary cessation of VKA in patients receiving VKA for treatment of VTE with INR >4.5 but <10 and without clinically relevant bleeding (conditional recommendation based on very low certainty in the evidence).
JUSTIFICATION	The guideline panel was unable to determine whether there was net benefit or harm associated with administration of oral vitamin K, but given the high cost of prescription oral vitamin K tablets and the variable vitamin K content of available over-the-counter products the panel conditionally recommends against administering oral vitamin K.

SUBGROUP CONSIDERATIONS	Administration of oral vitamin K might be considered in patients at high risk of developing bleeding complications (e.g. recent surgical procedure) or in situations where the INR is expected to be prolonged for a longer period of time (e.g. presence of interacting drugs or very low weekly VKA dose requirement).
IMPLEMENTATION CONSIDERATIONS	No implementation considerations.
MONITORING AND EVALUATION	No monitoring and evaluation considerations.
RESEARCH PRIORITIES	The panel identified the following additional research questions: 1) Is withholding VKA alone a safe and effective option in patients presenting with INR >10.0 in the absence of bleeding? 2) What is the minimum amount of oral vitamin K required to reverse the hypoprothrombinemic effect of VKA? 3) Can dietary sources of vitamin K (e.g. broccoli, spinach, etc.) be used to manage excessive VKA anticoagulation in non-bleeding patients?

References for Evidence to Decision (EtD) table

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Appendix – Evidence Profile

Q14. In patients receiving VKA for treatment of VTE with INR >4.5 but <10 and without clinically relevant bleeding should temporary cessation of VKA plus administration of vitamin K vs. temporary cessation of VKA alone be used?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**temporary cessation of VKA plus administration of vitamin K**	**temporary cessation of VKA alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality (follow up: range 30 days to 90 days; assessed with: All cause mortality)												
3 [1-3]	randomised trials	not serious	not serious	not serious	serious [a]	none	16/421 (3.8%)	13/439 (3.0%)	RR 1.24 (0.62 to 2.47)	**7 more per 1,000** (from 11 fewer to 44 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Major bleeding (follow up: mean 90 days; assessed with: Fatal bleeding or bleeding that required blood transfusion or admission)												
2 [2, 3]	randomised trials	not serious	not serious	not serious	serious [a]	none	10/392 (2.6%)	4/409 (1.0%)	RR 2.43 (0.81 to 7.27)	**14 more per 1,000** (from 2 fewer to 61 more)	⊕⊕⊕◯ MODERATE	CRITICAL
PE – Moderate severity - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
DVT in the upper leg — Moderate severity (follow up: mean 3 months; assessed with: Any DVT)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**temporary cessation of VKA plus administration of vitamin K**	**temporary cessation of VKA alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 [3]	randomised trials	not serious	not serious [b]	not serious	serious [a]	none	0/45 (0.0%)	1/44 (2.3%)	RR 0.32 (0.01 to 8.04)	**15 fewer per 1,000** (from 23 fewer to 160 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Quality of Life Impairment - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Emergency room visit - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Hospitalization - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Thromboembolism (follow up: mean 90 days; assessed with: Any thromboembolism)												
2 [2, 3]	randomised trials	not serious	not serious	not serious	serious [a]	none	5/392 (1.3%)	4/409 (1.0%)	RR 1.29 (0.35 to 4.78)	**3 more per 1,000** (from 6 fewer to 37 more)	⊕⊕⊕◯ MODERATE	NOT IMPORTANT
Proportion who reached goal INR (follow up: mean 1 days; assessed with: INR goal ranges included: INR 1.8-3.2; INR 2.3-4.5; and INR 2.0-4.0)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	temporary cessation of VKA plus administration of vitamin K	temporary cessation of VKA alone	Relative (95% CI)	Absolute (95% CI)		
4 [c 1-4]	randomised trials	serious [d]	serious [e]	not serious	serious [a]	none	218/493 (44.2%)	90/496 (18.1%)	RR 1.94 (0.88 to 4.27)	**171 more per 1,000** (from 22 fewer to 593 more)	⨁◯◯◯ VERY LOW	NOT IMPORTANT

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

Explanations

a. Lower and upper bounds of the 95% CI for the anticipated absolute effect include important benefit and important harm

b. Inconsistency cannot be determined as only one study reported the outcome

c. Crowther 2009 reported % of patients achieving INR 2.0-3.0, which was the target INR range for 78% of the study population

d. Four of the five studies did not blind patients and personnel, or outcome assessors

e. Non-overlapping confidence intervals and I^2=92%

References – Included Studies

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Question #15

Should **4-factor prothrombin complex concentrates (PCC)** vs. **fresh-frozen plasma (FFP)** be used **in addition to temporary cessation of VKA and intravenous vitamin K in patients with VKA-related life-threatening bleeding during treatment for VTE**?

POPULATION:	patients with VKA-related life-threatening bleeding during treatment for VTE who have temporarily stopped VKA and received intravenous vitamin K	**BACKGROUND:**	Patients presenting with acute major hemorrhage require rapid vitamin K antagonist reversal by prompt restoration of vitamin K–dependent coagulation factors. The first step is discontinuation of the drug and the administration of vitamin K; however, reversal can take several hours and vitamin K is not recommended as monotherapy for acute bleeding. Fresh Frozen Plasma (FFP) and 4-Factor Prothrombin Complex Concentrate (4-factor PCC) are two agents commonly used for acute reversal of vitamin K antagonists.
INTERVENTION:	4-factor prothrombin complex concentrates (PCC)		
COMPARISON:	Fresh-frozen plasma (FFP)		
MAIN OUTCOMES:	Mortality; Major bleeding; Volume overload; PE – Moderate severity; DVT in the upper leg — Moderate severity; Quality of Life Impairment; Proportion of patients who reached goal INR; Any thromboembolism;		
SETTING:	Inpatient		
PERSPECTIVE:	Clinical recommendation - Population perspective		

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Patients presenting with acute major hemorrhage require rapid vitamin K antagonist reversal by prompt restoration of vitamin K–dependent coagulation factors. The first step is discontinuation of the drug and the administration of vitamin K; however, reversal can take several hours and vitamin K is not recommended as monotherapy for acute bleeding. Fresh Frozen Plasma (FFP) and 4-Factor Prothrombin Complex Concentrate (4-factor PCC) are two agents commonly used for acute reversal of vitamin K antagonists.	

DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	For research evidence on Desirable and Undesirable anticipated effects, as well as the certainty of this evidence, see the **Evidence Profile** in the **Appendix**.	Individualized 4-factor PCC dosing can improve outcomes compared to fixed-dose 4-factor PCC. (Van Aart 2006) Panel used the average baseline risk group to make judgments. The intervention also reduced volume overload (an outcome that was not prioritized but, as other outcomes were balanced, the panel decided to prioritize this outcome).
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know		Bleeding risk increased with 4-factor PCC with low certainty of evidence but this conflicted with improvement in the surrogate measure of proportion of patients who achieved target INR levels with moderate certainty of evidence. VTE (both PE and DVT) was increased.

CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies		Evidence certainty for mortality was very low certainty, other prioritized outcomes were of low certainty. Percent of patients achieving target INR levels was moderate certainty.
VALUES	**Is there important uncertainty about or variability in 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	**Utility related information - the relative importance of outcomes** *Relative importance of the outcomes on a scale 0.00-1.00 with 1.00 indicating a patient comparing the outcome with being in 'Full health' and 0.00 comparing the outcome with being 'Dead'* <u>Our systematic review found that the relative importance of the outcomes is as follows:</u> - Pulmonary embolism: 0.63-0.93 (different methods) [1-3] - Deep vein thrombosis: 0.64-0.99 (different methods) [1-5] - Deep vein thrombosis patients' own current health: 0.95 (Time trade off) [3] - Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) [1, 3] - Muscular bleeding: 0.76 (time trade off) [3] - Minor intracranial bleeding event: 0.75 (standard gamble) [1] - Major intracranial bleeding event: 0.15 (standard gamble) [1] - Central nervous system bleeding: 0.29-0.60 (standard gamble) [6, 7] <u>Our survey among ASH guideline panel members found that</u>	

		the relative importance of QoL and TTR adherence is as follows: - Quality of life (QoL) impairment: 0.57 [SD 0.23] (ASH panels utility rating)	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		For average baseline risk groups, based on the low to very low certainty evidence, the panel judged that the benefits and harms with 4-factor PCC vs. FFP were balanced except for lower risk of volume overload with 4-factor PCC.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**The following economic analyses were identified:** Cost of 4-factor PCC and FFP Cost of 4-factor PCC: $2817 ± $646 for one course 4-PCC [8]; 4-factor PCC manufacturing pricing data was used to calculate $1.74/unit, while the average dose of 4-PCC is 2000 units, which equals $3480. [9] The total average cost of plasma was estimated at $409.62 per unit of FFP transfused, representing an average of $1,608.37 per inpatient transfused with FFP. [10] Although in the US the upfront cost is greater for administering 4-factor PCC rather than FFP, the mitigation of potentially severe transfusion-associated circulatory overload reactions requiring patient admittance to intensive care units greatly reduces the estimated per patient effective cost. In Europe the upfront cost for FFP is even more expensive than 4-factor PCC (approximately $904 vs. $618) hence accounting for transfusion-associated circulatory overload related ICU incidence with European figures makes the total estimated cost of administering 4-factor PCC 50.7% less	Additional clinical implications of higher volume overload from FFP may cause additional resource requirements. FFP requires additional monitoring time by staff that is administering the intervention. Of voting panel members, 6 voted for 'Moderate costs' and 3 voted for 'Negligible costs and savings'.

		expensive than FFP for the rapid reversal of vitamin K antagonists. [11] <u>Cost of clinical events</u> Cost of PE (event cost): $11,616 [12] Cost of recurrent VTE (outpatient, hospitalization, and pharmacy cost in 1-year following VTE event): $11,120 [13] Cost of bleeding: [13] - 6 months following DVT: $11,018 for patients with major bleed - Per-event cost estimated over variable follow-up (mean follow-up = 21.3 months): $22,885 for bleed event requiring hospitalization - Per-event cost: base case treatment of bleeds = $9,935	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ● Low ○ Moderate ○ High ○ No included studies		

COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	**The following cost-effectiveness analyses were identified:** A cost-effectiveness analysis based on a systematic review and UK National Health Service perspective showed that the cost of warfarin reversal was estimated to be ≤15% of the total cost of managing a patient after a life-threatening intracranial, gastrointestinal, or retroperitoneal hemorrhage. The cost per life-year gained with 4-factor PCC vs. FFP was estimated to range from £1,000 to £2,000, depending on hemorrhage type (ie, intracranial, gastrointestinal, or retroperitoneal). The cost per QALY gained with 4-factor PCC vs. FFP was estimated at £3,000 or less depending on hemorrhage type. [14]	
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified.	
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified.	Acceptability of using the intervention might depend on who is paying.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no	Substantial variability in reversal practices for bleeding on VKA was noted as a consideration for implementing 4-factor	Another feasibility issue considered by the panel was that 4-factor PCC takes less time to

	○ Probably yes ● Yes ○ Varies ○ Don't know	PCC use in VKA patients with a bleeding event was reported by two observational studies.[15, 16]	prepare and administer than FFP.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know	

	JUDGEMENT							IMPLICATIONS
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies	
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know	

Should 4-factor prothrombin complex concentrates (PCC) vs. fresh-frozen plasma (FFP) be used in addition to temporary cessation of VKA and intravenous vitamin K in patients with VKA-related life-threatening bleeding during treatment for VTE?

Type of recommendation

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○

Conclusions

RECOMMENDATION	The ASH guideline panel suggests using 4-factor PCC rather than FFP, in addition to temporary cessation of VKA and intravenous vitamin K in patients with VKA-related life-threatening bleeding during treatment for VTE (conditional recommendation based on very low certainty in the evidence).
JUSTIFICATION	Based on the body of available evidence, the panel favored 4-factor PCC over FFP because of ease of administration, the increased probability of achieving a near normalized INR, and less risk of volume overload.
SUBGROUP CONSIDERATIONS	Recommendation may differ based on type of bleeding patient (e.g. intracranial versus other types of bleeding).
IMPLEMENTATION CONSIDERATIONS	No implementation considerations.
MONITORING AND EVALUATION	No monitoring and evaluation considerations.
RESEARCH PRIORITIES	The panel identified the following additional research questions: 1) What is the cost-effectiveness of 4-factor PCC vs. FFP from the payer perspective in the US healthcare system? 2) What is the true magnitude of increased thromboembolic risk associated with 4-factor PCC administration?

References for Evidence to Decision (EtD) table

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Appendix – Evidence Profile

Q15. In patients with VKA-related life-threatening bleeding during treatment for VTE should 4-factor prothrombin complex concentrates (PCC) vs. fresh-frozen plasma (FFP) be used, in addition to temporary cessation of VKA and intravenous vitamin K?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	4-factor PCC	FFP	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: range 45 days to 90 days)												
3 [1-3]	randomised trials	not serious [a]	serious [b]	serious [c]	serious [d]	none	17/138 (12.3%)	18/145 (12.4%) [e,f]	RR 0.92 (0.37 to 2.28)	**10 fewer per 1,000** (from 78 fewer to 159 more)	⨁◯◯◯ VERY LOW	CRITICAL
								5.0% [e,f]		**4 fewer per 1,000** (from 32 fewer to 64 more)		
								54.0% [e,f]		**43 fewer per 1,000** (from 340 fewer to 691 more)		
PE – Moderate severity (follow up: mean 90 days; assessed with: Any PE)												
1 [3]	randomised trials	not serious	not serious [g]	serious [c]	serious [d]	none	4/27 (14.8%)	0/23 (0.0%)	RR 7.71 (0.44 to 136.11)	**15 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	CRITICAL
DVT in the upper leg — Moderate severity (follow up: mean 90 days; assessed with: Any DVT)												
1 [3]	randomised trials	not serious	not serious [g]	serious [c]	serious [d]	none	1/27 (3.7%)	0/23 (0.0%)	RR 2.57 (0.11 to 60.24)	**4 more per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	4-factor PCC	FFP	Relative (95% CI)	Absolute (95% CI)		
Any thromboembolism (follow up: range 45 days to 90 days; assessed with: Any thromboembolism)												
2 [2, 3]	randomised trials	not serious	not serious	serious [c]	serious [d]	none	15/130 (11.5%)	9/132 (6.8%)	RR 1.60 (0.70 to 3.62)	**41 more per 1,000** (from 20 fewer to 179 more)	⨁⨁◯◯ LOW	CRITICAL
Major bleeding (follow up: range 45 days to 90 days; assessed with: haematoma expansion, or intracranial haemorrhage, or subarachnoid haemorrhage)												
2 [2, 3]	randomised trials	serious [h]	not serious	not serious	serious [d]	none	18/130 (13.8%)	12/132 (9.1%) [i,j]	RR 1.34 (0.78 to 2.29)	**31 more per 1,000** (from 20 fewer to 117 more)	⨁⨁◯◯ LOW	CRITICAL
								5.0% [i,j]		**17 more per 1,000** (from 11 fewer to 65 more)		
								45.0% [i,j]		**153 more per 1,000** (from 99 fewer to 581 more)		
Quality of Life Impairment (follow up: mean 90 days; assessed with: EQ-5D questionnaire)												
1 [3]	randomised trials	not serious	not serious [g]	serious [c]	serious [d]	none	One RCT assessed quality of life impairment using the EQ-5D self report Questionnaire. The PCC group scored higher than the FFP group with a difference of -0·7 (95%CI: –5·6 to 4·2); the difference was not statistically signficant.				⨁⨁◯◯ LOW	CRITICAL
Proportion of patients who reached goal INR (follow up: range 0.5 hours to 3 hours; assessed with: Goal INR defined as ≤1.2 in Steiner 2016, and ≤1.3 in Serode 2013)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	4-factor PCC	FFP	Relative (95% CI)	Absolute (95% CI)		
2 [2, 3]	randomised trials	not serious	not serious	serious [c]	not serious	none	79/125 (63.2%)	12/127 (9.4%) [k]	RR 6.66 (3.82 to 11.61)	**535 more per 1,000** (from 266 more to 1,000 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
								43.9% [k]		**1,000 more per 1,000** (from 1,000 more to 1,000 more)		
Volume overload												
2 [1, 2]	randomised trials	serious [l]	not serious	not serious	serious [m]	none	5/108 (4.6%)	19/117 (16.2%)	RR 0.34 (0.13 to 0.85)	**107 fewer per 1,000** (from 24 fewer to 141 fewer)	⨁⨁◯◯ LOW	IMPORTANT

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

Explanations

a. Two of the three RCTs were not blinded, but mortality unlikely to be biased

b. I2 = 50%

c. Indications for VKA were either not stated or included a mix whereby a minority had VTE as indication

d. Lower and upper bounds of the 95% CI for the anticipated absolute effect include important benefit and important harm

e. Low baseline risk from observational study with the lowest risk for the FFP group (Karaca 2014).[4] Comparative observational studies were identified in a systematic review.

f. High baseline risk from observational study with the highest risk for the FFP group (Majeed 2014).[5] Comparative observational studies were identified in a systematic review.

g. Inconsistency cannot be determined as only one RCT reported the outcome

h. RCTs were not blinded

i. Low baseline risk from observational study with the lowest risk for the FFP group (Ortmann 2015).[6] Comparative observational studies were identified in a systematic review.

j. High baseline risk from observational study with the highest risk for the FFP group (Kuramatsu 2015).[7] Comparative observational studies were identified in a systematic review.

k. High baseline risk from observational study with the highest risk for the FFP group (Rowe 2016).[8] Comparative observational studies were identified in a systematic review.

l. Studies were not blinded

m. Lower and upper bounds of the 95% CI for the anticipated absolute effect include highly important benefit and somewhat important benefit

References – Included RCTs

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References – Studies for Baseline Risk

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Question #16

Should **temporary cessation of dabigatran plus idarucizumab administration** vs. **temporary cessation of dabigatran alone** be used in **patients with dabigatran related life-threatening bleeding during treatment for VTE**?

POPULATION:	patients with dabigatran related life-threatening bleeding during treatment for VTE	**BACKGROUND:**	Dabigatran has been shown to be safe and effective for the treatment of venous thromboembolism. However, as with any anticoagulant, patients taking dabigatran are at increased risk of major bleeding. When major bleeding occurs, dabigatran is typically stopped. Administering the reversal agent idarucizumab might accelerate anticoagulation reversal and prevent the bleeding from progressing to more serious or fatal bleeding.
INTERVENTION:	temporary cessation of dabigatran plus idarucizumab administration		
COMPARISON:	temporary cessation of dabigatran alone		
MAIN OUTCOMES:	Mortality; DVT in the upper leg — Moderate severity; PE – Moderate severity; Thromboembolism; Major bleeding; Quality of Life Impairment;		
SETTING:	Inpatient		
PERSPECTIVE:	Clinical recommendation - Population perspective		

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Dabigatran has been shown to be safe and effective for the treatment of venous thromboembolism. However, as with any anticoagulant, patients taking dabigatran are at increased risk of major bleeding. When major bleeding occurs, dabigatran is typically stopped. Administering the reversal agent idarucizumab might accelerate anticoagulation reversal and prevent the bleeding from progressing to more serious or fatal bleeding.	

DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	For research evidence on Desirable and Undesirable anticipated effects, as well as the certainty of this evidence, see the **Evidence Profile** in the **Appendix**.	No study reported a direct comparison.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know		
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies		Very low certainty evidence, primarily due to serious indirectness in absence of direct comparisons, as well as risk of bias and imprecision.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability	**Utility related information - the relative importance of outcomes** *Relative importance of the outcomes on a scale 0.00-1.00 with 1.00 indicating a patient comparing the outcome with being in 'Full health' and 0.00 comparing the outcome with being 'Dead'*	

	○ No important uncertainty or variability	Our systematic review found that the relative importance of the outcomes is as follows: - Pulmonary embolism: 0.63-0.93 (different methods) [1-3] - Deep vein thrombosis: 0.64-0.99 (different methods) [1-5] - Deep vein thrombosis patients' own current health: 0.95 (Time trade off) [3] - Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) [1, 3] - Muscular bleeding: 0.76 (time trade off) [3] - Minor intracranial bleeding event: 0.75 (standard gamble) [1] - Major intracranial bleeding event: 0.15 (standard gamble) [1] - Central nervous system bleeding: 0.29-0.60 (standard gamble) [6, 7]	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		Very low certainty evidence indicates a potentially reduced risk of further bleeding and mortality.

RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**The following economic analyses were identified:** <u>Cost of idarucizumab</u> Cost of idarucizumab in the US: the wholesale acquisition cost of two 2.5 g vials of idarucizumab is currently $3482.50 [8] <u>Resource use in patients with major bleeding receiving idarucizumab</u> Blood products or pro-hemostatic agents were given to 63% of patients. An overnight hospital stay was reported for 82% of patients with median length of stay of 7 (1–71) bed-days. 33% of patients was admitted to the ICU for at least 1 day. [9] <u>Cost of clinical events</u> Cost of PE (event cost): $11,616 [10] Cost of recurrent VTE (outpatient, hospitalization, and pharmacy cost in 1-year following VTE event): $11,120 [11] Cost of bleeding: [11] - 6 months following DVT: $11,018 for patients with major bleed - Per-event cost estimated over variable follow-up (mean follow-up = 21.3 months): $22,885 for bleed event requiring hospitalization - Per-event cost: base case treatment of bleeds = $9,935	Cost evaluation of health benefits is uncertain because the health benefits are uncertain. Judgement is based on drug cost alone. One panel member voted for 'Large costs'.

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ● Low ○ Moderate ○ High ○ No included studies		
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	The panel could not provide a judgment due to a lack of cost-effectiveness studies.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified.	Most hospitals are likely to stock the medication. Availability of the intervention to patients will depend on where they are hospitalized for their life threatening bleeding.

ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified.	Payers may be reluctant to cover the intervention. Hospitals may feel that if they do not provide the intervention this may lead to liability issues.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence identified.	The panel judged that there are no practical barriers to implementing the intervention in hospitals.

Summary of judgements (consensus)

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know	

	JUDGEMENT							IMPLICATIONS
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know	Probably favors temporary cessation of dabigatran plus idarucizumab administration
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	Probably favors temporary cessation of dabigatran alone
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies	Probably favors temporary cessation of dabigatran alone
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**	Favors neither intervention
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know	Favors neither intervention
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	Probably favors temporary cessation of dabigatran plus

	JUDGEMENT							IMPLICATIONS
								idarucizumab administration
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know	Favors temporary cessation of dabigatran plus idarucizumab administration

Should temporary cessation of dabigatran plus idarucizumab administration vs. temporary cessation of dabigatran alone be used in patients with dabigatran related life-threatening bleeding during treatment for VTE?

Type of recommendation

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○

Conclusions

RECOMMENDATION	The ASH guideline panel suggests using idarucizumab in addition to temporary cessation of dabigatran rather than no idarucizumab in patients with dabigatran related life-threatening bleeding during treatment for VTE (conditional recommendation based on very low certainty in the evidence). This recommendation does not apply to individuals with non-life-threatening bleeding. Remarks: Cost of the drugs is the only information directly available. Reduced cost of bleeding are not considered because the degree of bleeding risk reduction is uncertain.
JUSTIFICATION	The guideline panel determined that there is very low certainty evidence for a net health benefit from using idarucizumab to manage life-threatening bleeding in patients receiving dabigatran therapy for VTE. Based on the body of available evidence, it is possible that idarucizumab reduces the risk of developing recurrent and/or worsening bleeding and possibly also mortality risk. While cost of the drug was deemed moderate, this cost may be offset by reducing bleeds although this is unknown at the present time. Some panel members were concerned about the possibility of VTE increased risk. Further, the panel felt that this recommendation does not apply to patients with non-life-threatening bleeding.
SUBGROUP CONSIDERATIONS	The recommendation applies to life-threatening bleeding or uncontrolled bleeding requiring an urgent intervention.
IMPLEMENTATION CONSIDERATIONS	No implementation considerations.
MONITORING AND EVALUATION	No monitoring and evaluation considerations.
RESEARCH PRIORITIES	The panel identified the following additional research questions: 1) What clinical parameters define the need for intervention with idarucizumab over withholding dabigatran alone? 2) What is the comparative effectiveness of idarucizumab in real-world patients presenting with potentially life-threatening dabigatran associated bleeding?

References for Evidence to Decision (EtD) table

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Appendix – Evidence Profile

Q16. In patients with dabigatran related life-threatening bleeding during treatment for VTE should temporary cessation of dabigatran plus idarucizumab administration vs. temporary cessation of dabigatran alone be used?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	temporary cessation of dabigatran plus idarucizumab administration	temporary cessation of dabigatran alone	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: range 3 days to 30 days)												
3 [1-3]	observational studies	very serious [a]	not serious [b]	very serious [c]	serious [d]	none	41/303 (13.5%)	2/7 (28.6%)	RR 0.49 (0.15 to 1.62) [e]	**146 fewer per 1,000** (from 177 more to 243 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
DVT in the upper leg — Moderate severity (follow up: mean 30 days; assessed with: Any DVT)												
1 [3]	observational studies	not serious [f]	not serious [b]	very serious [c,g]	serious [h]	none	6/301 (2.0%)		not estimable		⨁◯◯◯ VERY LOW	CRITICAL
PE – Moderate severity (follow up: mean 30 days; assessed with: Any PE)												
1 [3]	observational studies	not serious [f]	not serious [b]	very serious [c,g]	serious [h]	none	4/301 (1.3%)		not estimable		⨁◯◯◯ VERY LOW	CRITICAL
Thromboembolism (follow up: mean 30 days; assessed with: Any thromboembolism)												
1 [3]	observational studies	not serious [f]	not serious [b]	very serious [c,g]	serious [h]		14/301 (4.7%)		not estimable		-	
Major bleeding (follow up: range 3 hours to 24 hours; assessed with: Recurrent or continued bleeding)												
3 [1-3]	observational studies	very serious [a]	not serious [b]	not serious	serious [d]	none	10/303 (3.3%)	2/7 (28.6%)	RR 0.13 (0.03 to 0.47) [i]	**249 fewer per 1,000** (from 151 fewer to 277 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of Life Impairment - not reported												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	temporary cessation of dabigatran plus idarucizumab administration	temporary cessation of dabigatran alone	Relative (95% CI)	Absolute (95% CI)		
-	-	-	-	-	-	-					-	CRITICAL

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

Explanations

a. Very high risk of confounding as the event rate for the intervention group [1,3] came from different studies than the event rate for the control group [2] . No adjustment for important differences in study designs, populations and outcome assessment.

b. Inconsistency cannot be determined as no studies reported a direct comparison

c. Indication for VKA was mainly atrial fibrillation, few patients had VTE as indication

d. Lower and upper bounds of the 95% CI for the anticipated absolute effect include important benefit and important harm

e. Comparison based on the pooled event rate for the intervention group and a single study control group. The weighted pooled event rate for the intervention group was calculated by transforming all study event rates using the Freeman-Tukey arcsine transformation, calculating a pooled estimate of the transformed event rates, and back transforming this pooled estimate to a pooled event rate. (Freeman-Tukey 1950). The weighted pooled event rate for the intervention group was 13.7% (95% CI: 10.1-17.8%), which is different from the overall unweighted event rate of 13.5% (41/303). Therefore, the weighted event rate of 13.7% was used to calculate the relative effect and anticipated absolute effect.

f. Risk of bias cannot be assessed because the study did not report a comparison.

g. The study did not report a direct comparison, but only the event rate for the intervention group.

h. Small number of events

i. Comparison based on the pooled event rate for the intervention group and a single study control group. The weighted pooled event rate for the intervention group was calculated by transforming all study event rates using the Freeman-Tukey arcsine transformation, calculating a pooled estimate of the transformed event rates, and back transforming this pooled estimate to a pooled event rate. (Freeman-Tukey 1950). The weighted pooled event rate for the intervention group was 3.5% (95% CI: 1.7-5.9%), which is different from the overall unweighted event rate of 3.3% (10/303). Therefore, the weighted event rate of 3.5% was used to calculate the relative effect and anticipated absolute effect.

References – Included Studies

1. Held V, Eisele P, Eschenfelder CC, Szabo K. Idarucizumab as Antidote to Intracerebral Hemorrhage under Treatment with Dabigatran. Case Rep Neurol. 2016;8(3):224-8.
2. Kumar R, Smith RE, Henry BL. A Review of and Recommendations for the Management of Patients With Life-Threatening Dabigatran-Associated Hemorrhage: A Single-Center University Hospital Experience. J Intensive Care Med. 2015;30(8):462-72.
3. Pollack CV, Jr., Reilly PA, van Ryn J, Eikelboom JW, Glund S, Bernstein RA, et al. Idarucizumab for Dabigatran Reversal - Full Cohort Analysis. N Engl J Med. 2017;377(5):431-41.

Question #17a

Should **temporary cessation of oral direct Xa inhibitor plus 4-factor prothrombin complex concentrates (PCC) administration** vs. **temporary cessation of oral direct Xa inhibitor alone** be used in **patients with oral direct Xa inhibitor related life-threatening bleeding during treatment for VTE**?

POPULATION:	patients with oral direct Xa inhibitor related life-threatening bleeding during treatment for VTE
INTERVENTION:	temporary cessation of oral direct Xa inhibitor plus 4-factor prothrombin complex concentrates (PCC) administration
COMPARISON:	temporary cessation of oral direct Xa inhibitor alone
MAIN OUTCOMES:	Mortality; PE - Moderate Severity; DVT in the upper leg - Moderate severity; Major Bleeding; Quality of Life Impairment;
SETTING:	Inpatient
PERSPECTIVE:	Clinical recommendation - Population perspective

BACKGROUND: Factor Xa inhibitors have been shown to be safe and effective for the treatment of venous thromboembolism. However, as with any anticoagulant, patients taking direct oral factor Xa inhibitors are at increased risk of major bleeding. When a life-threatening bleeding occurs, the direct factor Xa inhibitor is stopped to reverse the bleeding. Additional medications might be applied to accelerate this reversal. Prothrombin complex concentrates (PCCs) might be a useful reversal agent..

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Factor Xa inhibitors have been shown to be safe and effective for the treatment of venous thromboembolism. However, as with any anticoagulant, patients taking direct oral factor Xa inhibitors are at increased risk of major bleeding. When a life-threatening bleeding occurs, the direct factor Xa inhibitor is stopped to reverse the bleeding. Additional medications might be applied to accelerate this reversal. Prothrombin complex concentrates (PCCs) might be a useful reversal agent.	
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate	For research evidence on Desirable and Undesirable anticipated effects, as well as the certainty of this evidence, see the **Evidence Profile** in the **Appendix**.	The panel could not make a judgement in the absence of control group data.

	○ Large ○ Varies ● Don't know		
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know		The panel could not make a judgement in the absence of control group data.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies		
VALUES	**Is there important uncertainty about or variability in 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	**Utility related information - the relative importance of outcomes** *Relative importance of the outcomes on a scale 0.00-1.00 with 1.00 indicating a patient comparing the outcome with being in 'Full health' and 0.00 comparing the outcome with being 'Dead'* <u>Our systematic review found that the relative importance of the outcomes is as follows:</u> - Pulmonary embolism: 0.63-0.93 (different methods) [1-3] - Deep vein thrombosis: 0.64-0.99 (different methods) [1-5]	

		- Deep vein thrombosis patients' own current health: 0.95 (Time trade off) [3] - Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) [1, 3] - Muscular bleeding: 0.76 (time trade off) [3] - Minor intracranial bleeding event: 0.75 (standard gamble) [1] - Major intracranial bleeding event: 0.15 (standard gamble) [1] - Central nervous system bleeding: 0.29-0.60 (standard gamble) [6, 7]	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know		The panel could not make a judgement in the absence of control group data. However it was noted that bleeding either worsened or did not improve in 40% of patients receiving 4-factor PCC.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**The following economic analyses were identified:** <u>Cost of 4-factor PCC</u> COst of 4-factor PCC was $2,817 ± $646 USD for one treatment course. [8] 4-factor PCC manufacturing pricing data was used to calculate $1.74/unit, while the average dose of 4-factor PCC is 2000 units, which equals $3,480 USD. [9] <u>Cost of clinical events</u> Cost of PE (event cost): $11,616 [10] Cost of recurrent VTE (outpatient, hospitalization, and pharmacy cost in 1-year following VTE event): $11,120 [11] Cost of bleeding: [11] - 6 months following DVT: $11,018 for patients with major bleed	

		- Per-event cost estimated over variable follow-up (mean follow-up = 21.3 months): $22,885 for bleed event requiring hospitalization - Per-event cost: base case treatment of bleeds = $9,935	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ● Low ○ Moderate ○ High ○ No included studies		
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	The panel could not provide a judgment due to a lack of cost-effectiveness studies and lack of information on effects.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified.	

ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified.	The panel judged that the intervention is probably acceptable in case of life-threatening bleeding.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence identified.	The panel judged that the interventions is feasible at is currently being used for anticoagulation reversal.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**	
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**	
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies	

	JUDGEMENT							IMPLICATIONS
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**	
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**	
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know	

Should temporary cessation of oral direct Xa inhibitor plus 4-factor prothrombin complex concentrates (PCC) administration vs. temporary cessation of oral direct Xa inhibitor alone be used in patients with oral direct Xa inhibitor related life-threatening bleeding during treatment for VTE?

Type of recommendation

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	●	○	○	○

Conclusions

RECOMMENDATION	The ASH guideline panel suggests not using 4-factor PCC administration in addition to temporary cessation of oral direct Xa inhibitor in patients with life-threatening bleeding during treatment for VTE (conditional recommendation based on very low certainty in the evidence). Remark: one panel member abstained from voting and one panel member did not support this recommendation.
JUSTIFICATION	The panel made this judgement based on the absence of evidence for effects, evidence of worsening bleeding or lack of improvement in 40% of patients and moderate costs of administering the intervention. One panel member felt that in a life-threatening situation the experience and judgement of the prescriber would be the deciding factor.
SUBGROUP CONSIDERATIONS	No subgroup considerations.
IMPLEMENTATION CONSIDERATIONS	No implementation considerations.
MONITORING AND EVALUATION	No monitoring and evaluation considerations.
RESEARCH PRIORITIES	The panel identified the following additional research questions: 1) What clinical parameters define the need for intervention with 4-factor PCC over withholding oral direct Xa inhibitor alone? 2) What is the comparative effectiveness of 4-factor PCC in real-world patients presenting with potentially life-threatening oral direct Xa inhibitor associated bleeding vs. withholding direct Xa inhibitor alone?

References for Evidence to Decision (EtD) table

1. Hogg K, Kimpton M, Carrier M, Coyle D, Forgie M, Wells P. Estimating quality of life in acute venous thrombosis. JAMA internal medicine. 2013;173(12):1067-72.
2. Hogg K, Shaw J, Coyle D, Fallah P, Carrier M, Wells P. Validity of standard gamble estimated quality of life in acute venous thrombosis. Thrombosis research. 2014;134(4):819-25.
3. Locadia M, Bossuyt PM, Stalmeier PF, Sprangers MA, van Dongen CJ, Middeldorp S, et al. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thrombosis and haemostasis. 2004;92(6):1336-41.
4. Marvig CL, Verhoef TI, de Boer A, Kamali F, Redekop K, Pirmohamed M, et al. Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants. Thrombosis research. 2015;136(1):69-75.
5. Utne KK, Tavoly M, Wik HS, Jelsness-Jorgensen LP, Holst R, Sandset PM, et al. Health-related quality of life after deep vein thrombosis. SpringerPlus. 2016;5(1):1278.
6. Lenert LA, Soetikno RM. Automated computer interviews to elicit utilities: potential applications in the treatment of deep venous thrombosis. Journal of the American Medical Informatics Association : JAMIA. 1997;4(1):49-56.
7. O'Meara JJ, 3rd, McNutt RA, Evans AT, Moore SW, Downs SM. A decision analysis of streptokinase plus heparin as compared with heparin alone for deep-vein thrombosis. The New England journal of medicine. 1994;330(26):1864-9.
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9. Cleary KA, Waits LP, Hohenlohe PA. Development and characterization of fourteen novel microsatellite markers for the chestnut short-tailed fruit bat (Carollia castanea), and cross-amplification to related species. PeerJ. 2016;4:e2465.
10. Saunders RJ, Ozols AA. Cost burden of venous thromboembolism and its prophylaxis in the United States. 2016.
11. Grosse SD, Nelson RE, Nyarko KA, Richardson LC, Raskob GE. The economic burden of incident venous thromboembolism in the United States: A review of estimated attributable healthcare costs. Thromb Res. 2016;137:3-10.

Appendix – Evidence Profile

Q17a. In patients with oral direct Xa inhibitor related life-threatening bleeding during treatment for VTE should temporary cessation of oral direct Xa inhibitor plus 4-factor prothrombin complex concentrates (PCC) administration vs. temporary cessation of oral direct Xa inhibitor alone be used?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	temporary cessation of oral direct Xa inhibitor plus 4-factor PCC administration	temporary cessation of oral direct Xa inhibitor alone	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: range 9 days to 30 days)[a]												
4 [1-4]	observational studies	not serious [b]	serious [c]	very serious [d]	serious [e]	none	29/102 (28.4%)		not estimable		⨁◯◯◯ VERY LOW	CRITICAL
PE - Moderate Severity (follow up: range 9 days to 30 days; assessed with: Any thromboembolism)												
2 [1, 4]	observational studies	not serious [b]	serious [c]	very serious [d]	serious [f]	none	2/93 (2.2%)		not estimable		⨁◯◯◯ VERY LOW	CRITICAL
DVT in the upper leg - Moderate severity (follow up: mean 30 days; assessed with: Any thromboembolism)												
2 [1, 4]	observational studies	not serious [b]	serious [c]	very serious [d]	serious [f]	none	2/93 (2.2%)		not estimable		⨁◯◯◯ VERY LOW	CRITICAL
Major Bleeding (follow up: range 9 days to 30 days; assessed with: Ineffective management of major bleeding)[a]												
4 [1-4]	observational studies	not serious [b]	serious [c]	very serious [d]	serious [e]	none	40/99 (40.4%)		not estimable		⨁◯◯◯ VERY LOW	CRITICAL
Quality of Life Impairment - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Three studies (Pahs 2015, Senger 2016, Yoshimura 2017) reported outcome during hospitalization, of which Yoshimura reported a median hospitalization of 9 days.

b. No comparison group, risk of bias cannot be assessed.

c. Important differences in the reported event rates across studies.

d. The study did not report a direct comparison, but only the event rate for the intervention group. Main indication for oral direct Xa inhibitor treatment was atrial fibrillation, a minority had VTE as indication.

e. The weighted pooled event rate was 19.0% with a large confidence interval (95% CI: 4.0-41.4%).

f. The weighted pooled event rate was 2.9% with a large confidence interval (95% CI: 0.5-7.2%)

g. The weighted pooled event rate was 39.9% with a large confidence interval (95% CI: 17.6-64.7%).

References – Included studies

1. Majeed A, Agren A, Holmstrom M, Bruzelius M, Chaireti R, Odeberg J, et al. Management of rivaroxaban- or apixaban-associated major bleeding with prothrombin complex concentrates: a cohort study. Blood. 2017;130(15):1706-12.
2. Pahs L, Beavers C, Schuler P. The Real-World Treatment of Hemorrhages Associated With Dabigatran and Rivaroxaban: A Multicenter Evaluation. Crit Pathw Cardiol. 2015;14(2):53-61.
3. Senger S, Keiner D, Hendrix P, Oertel J. New Target-Specific Oral Anticoagulants and Intracranial Bleeding: Management and Outcome in a Single-Center Case Series. World Neurosurg. 2016;88:132-9.
4. Yoshimura S, Sato S, Todo K, Okada Y, Furui E, Matsuki T, et al. Prothrombin complex concentrate administration for bleeding associated with non-vitamin K antagonist oral anticoagulants: The SAMURAI-NVAF study. J Neurol Sci. 2017;375:150-7.

Question #17b

Should **temporary cessation of oral direct Xa inhibitor plus andexanet** vs. **temporary cessation of oral direct Xa inhibitor alone** be used in **patients with oral direct Xa inhibitor related life-threatening bleeding during treatment for VTE**?

POPULATION:	patients with oral direct Xa inhibitor related life-threatening bleeding during treatment for VTE
INTERVENTION:	temporary cessation of oral direct Xa inhibitor plus andexanet
COMPARISON:	temporary cessation of oral direct Xa inhibitor alone
MAIN OUTCOMES:	Mortality; PE - Moderate Severity; DVT in the upper leg - Moderate severity; Major Bleeding; Quality of Life Impairment;
SETTING:	Inpatient
PERSPECTIVE:	Clinical recommendation - Population perspective

BACKGROUND: Factor Xa inhibitors have been shown to be safe and effective for the treatment of venous thromboembolism. However, as with any anticoagulant, patients taking direct oral factor Xa inhibitors are at increased risk of major bleeding. When major bleeding occurs, the direct factor Xa inhibitor is stopped to reverse the bleeding. Andexanet alfa has been designed to specifically reverse the effects of both direct and indirect factor Xa inhibitors.

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Factor Xa inhibitors have been shown to be safe and effective for the treatment of venous thromboembolism. However, as with any anticoagulant, patients taking direct oral factor Xa inhibitors are at increased risk of major bleeding. When major bleeding occurs, the direct factor Xa inhibitor is stopped to reverse the bleeding. Andexanet alfa has been designed to specifically reverse the effects of both direct and indirect factor Xa inhibitors.	
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate	For research evidence on Desirable and Undesirable anticipated effects, as well as the certainty of this evidence, see the **Evidence Profile** in the **Appendix**.	The panel could not make a judgement in the absence of a control group.

	○ Large ○ Varies ● Don't know		
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know		The panel could not make a judgement in the absence of a control group.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies		Very low quality evidence due to the absence of a control group and few events in the intervention group.
VALUES	**Is there important uncertainty about or variability in 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	**Utility related information - the relative importance of outcomes** *Relative importance of the outcomes on a scale 0.00-1.00 with 1.00 indicating a patient comparing the outcome with being in 'Full health' and 0.00 comparing the outcome with being 'Dead'* <u>Our systematic review found that the relative importance of the outcomes is as follows:</u> - Pulmonary embolism: 0.63-0.93 (different methods) [1-3] - Deep vein thrombosis: 0.64-0.99 (different methods) [1-5] - Deep vein thrombosis patients' own current health: 0.95 (Time trade off) [3]	

		- Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) [1, 3] - Muscular bleeding: 0.76 (time trade off) [3] - Minor intracranial bleeding event: 0.75 (standard gamble) [1] - Major intracranial bleeding event: 0.15 (standard gamble) [1] - Central nervous system bleeding: 0.29-0.60 (standard gamble) [6, 7]	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know		The panel could not make a judgement as the effects of the intervention vs. the comparator were not known.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**The following economic analyses were identified:** <u>Cost of andexanet</u> Cost of andexanet in the US is currently unknown <u>Cost of clinical events</u> Cost of PE (event cost): $11,616 [8] Cost of recurrent VTE (outpatient, hospitalization, and pharmacy cost in 1-year following VTE event): $11,120 [9] Cost of bleeding: [9] - 6 months following DVT: $11,018 for patients with major bleed - Per-event cost estimated over variable follow-up (mean follow-up = 21.3 months): $22,885 for bleed event requiring hospitalization - Per-event cost: base case treatment of bleeds = $9,935	Making an assumption based on expert input, the cost was anticipated to be high. Of voting panel members, 8 voted for 'Large costs', 1 for 'Moderate costs' and 2 for 'Don't know'.

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies		
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research identified.	
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know	No research evidence identified.	The panel assumed that the cost will be high, but we don't know the exact cost and availability among hospitals until the drug comes to market.

ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ● Don't know	No research evidence identified.	The panel assumed that the cost will be high, but we don't know the exact cost and availability among hospitals until the drug comes to market.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified.	The panel judged that administration of the intervention will be somewhat complicated, but probably feasible in the hospital setting.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**	
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**	
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies	

	JUDGEMENT							IMPLICATIONS
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**	
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	**Don't know**	
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Conclusions

Should temporary cessation of oral direct Xa inhibitor plus andexanet vs. temporary cessation of oral direct Xa inhibitor alone be used in patients with oral direct Xa inhibitor related life-threatening bleeding during treatment for VTE?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○
RECOMMENDATION	The ASH guideline panel suggests using andexanet in addition to temporary cessation of oral direct Xa inhibitor rather than no andexanet in patients with direct Xa inhibitor related life-threatening bleeding during treatment for VTE (conditional recommendation based on very low certainty in the evidence). In an official vote, 6 panel members voted for a Conditional recommendation for using andexanet, 1 voted for a Conditional recommendation against using andexanet, and 3 panel members abstained from voting. Remarks: Andexanet was not approved by regulatory agencies at the time of the creation of this guideline. Rapid update is required.				
JUSTIFICATION	Based on the absence of data for the comparator, very low certainty evidence from one observational study, the assumed high cost of the intervention, with the probable acceptability and feasibility of the intervention, the panel could not come to unanimous decision. Voting provided a conditional recommendation for the intervention, primarily based on the evidence for drug reversal and biological plausibility of preventing worsening of bleeding for drugs that do not have an established reversal agent.				
SUBGROUP CONSIDERATIONS	This recommendation does not apply to individuals with non-life-threatening bleeding.				
IMPLEMENTATION CONSIDERATIONS	No implementation considerations.				
MONITORING AND EVALUATION	No monitoring and evaluation considerations.				
RESEARCH PRIORITIES	The panel identified the following research priorities:				

	1) This guideline question has no comparative data, which should be the primary aim of future research. 2) Cost-effectiveness modeling based on comparative data and the actual costs of the intervention.

References for Evidence to Decision (EtD) table

1. Hogg K, Kimpton M, Carrier M, Coyle D, Forgie M, Wells P. Estimating quality of life in acute venous thrombosis. JAMA internal medicine. 2013;173(12):1067-72.
2. Hogg K, Shaw J, Coyle D, Fallah P, Carrier M, Wells P. Validity of standard gamble estimated quality of life in acute venous thrombosis. Thrombosis research. 2014;134(4):819-25.
3. Locadia M, Bossuyt PM, Stalmeier PF, Sprangers MA, van Dongen CJ, Middeldorp S, et al. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thrombosis and haemostasis. 2004;92(6):1336-41.
4. Marvig CL, Verhoef TI, de Boer A, Kamali F, Redekop K, Pirmohamed M, et al. Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants. Thrombosis research. 2015;136(1):69-75.
5. Utne KK, Tavoly M, Wik HS, Jelsness-Jorgensen LP, Holst R, Sandset PM, et al. Health-related quality of life after deep vein thrombosis. SpringerPlus. 2016;5(1):1278.
6. Lenert LA, Soetikno RM. Automated computer interviews to elicit utilities: potential applications in the treatment of deep venous thrombosis. Journal of the American Medical Informatics Association : JAMIA. 1997;4(1):49-56.
7. O'Meara JJ, 3rd, McNutt RA, Evans AT, Moore SW, Downs SM. A decision analysis of streptokinase plus heparin as compared with heparin alone for deep-vein thrombosis. The New England journal of medicine. 1994;330(26):1864-9.
8. Saunders RJ, Ozols AA. Cost burden of venous thromboembolism and its prophylaxis in the United States. 2016.
9. Grosse SD, Nelson RE, Nyarko KA, Richardson LC, Raskob GE. The economic burden of incident venous thromboembolism in the United States: A review of estimated attributable healthcare costs. Thromb Res. 2016;137:3-10.

Appendix – Evidence Profile

Q17b. In patients with oral direct Xa inhibitor related life-threatening bleeding during treatment for VTE should temporary cessation of oral direct Xa inhibitor plus andexanet vs. temporary cessation of oral direct Xa inhibitor alone be used?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	temporary cessation of oral direct Xa inhibitor plus andexanet	temporary cessation of oral direct Xa inhibitor alone	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: median 30 days)												
1 [1]	observational studies	not serious [a]	not serious [b]	very serious [c]	very serious [d]	none	10/67 (14.9%)		not estimable		⨁◯◯◯ VERY LOW	CRITICAL
PE - Moderate Severity (Andexanet) (follow up: mean 30 days; assessed with: Any PE)												
1 [1]	observational studies	not serious [a]	not serious [b]	very serious [c]	very serious [d]	none	1/67 (1.5%)		not estimable		⨁◯◯◯ VERY LOW	CRITICAL
DVT in the upper leg - Moderate severity (Andexanet) (follow up: mean 30 days; assessed with: Any DVT)												
1 [1]	observational studies	not serious [a]	not serious [b]	very serious [c]	very serious [d]	none	7/67 (10.4%)		not estimable		⨁◯◯◯ VERY LOW	CRITICAL
Major Bleeding (Andexanet) (follow up: mean 30 days; assessed with: poor or no hemostatic efficacy)												
1 [1]	observational studies	not serious [a]	not serious [b]	very serious [c]	very serious [d]	none	9/47 (19.1%)		not estimable		⨁◯◯◯ VERY LOW	CRITICAL
Quality of Life Impairment - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. No comparison group, risk of bias cannot be assessed

b. Inconsistency cannot be determined as the single study did not report a direct comparison

c. The study did not report a direct comparison, but only the event rate for the intervention group. Indication for VKA was atrial fibrillation, no VTE

d. Small number of events

References – Included Studies

1. Connolly SJ, Milling TJ, Jr., Eikelboom JW, Gibson CM, Curnutte JT, Gold A, et al. Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors. N Engl J Med. 2016;375(12):1131-41.

Question #18

Should **temporary cessation of LMWH or UFH plus protamine** vs. **temporary cessation of LMWH or UFH alone be used** be used in **patients with LMWH or UFH related life-threatening bleeding during treatment for VTE**?

POPULATION:	patients with LMWH or UFH related life-threatening bleeding during treatment for VTE
INTERVENTION:	temporary cessation of LMWH or UFH plus protamine
COMPARISON:	temporary cessation of LMWH or UFH alone be used
MAIN OUTCOMES:	Mortality; PE - Moderate severity; DVT in the upper leg - Moderate severity; Thromboembolism; Major Bleeding; Quality of life impairment; Duration of hospitalization;
SETTING:	Inpatient
PERSPECTIVE:	Clinical recommendation - Population perspective

BACKGROUND: Low molecular weight heparins (LMWHs) and unfractionated heparins (UFH) are frequently used at low doses for thromboprophylaxis and, at higher doses, for the initial treatment of venous thrombotic events (VTEs). Overall, the risk of major hemorrhage is estimated to be between 1 and 4% depending on the underlying disease, the intensity of anticoagulation, concomitant medication and duration of treatment. Protamine sulphate fully reverses the anticoagulant effect of UFH and partially reverses the anticoagulant effect of LMWH. Temporary cessation alone may be sufficient in bleeding patients given the relatively short half-lives of UFH and LMWH.

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Low molecular weight heparins (LMWHs) and unfractionated heparins (UFH) are frequently used at low doses for thromboprophylaxis and, at higher doses, for the initial treatment of venous thrombotic events (VTEs). Overall, the risk of major hemorrhage is estimated to be between 1 and 4% depending on the underlying disease, the intensity of anticoagulation, concomitant medication and duration of treatment. Protamine sulphate fully reverses the anticoagulant effect of UFH and partially reverses the anticoagulant effect of LMWH. Temporary cessation alone may be sufficient in bleeding patients given the relatively short half-lives of UFH and LMWH.	

DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	For research evidence on Desirable and Undesirable anticipated effects, as well as the certainty of this evidence, see the **Evidence Profile** in the **Appendix**.	As most studies did not specify if 'heparin' included UFH or LMWH, we could not analyze according to heparin subgroup.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		As most studies did not specify if 'heparin' included UFH or LMWH, we could not analyze according to heparin subgroup.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies		Very low certainty evidence primarily due to very serious indirectness, as the included studies were patients receiving protamine for LMWH/UFH when undergoing invasive procedures, not for major bleeding in VTE patients.
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability	**Utility related information - the relative importance of outcomes** *Relative importance of the outcomes on a scale 0.00-1.00 with 1.00 indicating a patient comparing the outcome with being in 'Full health' and 0.00 comparing the outcome with being 'Dead'*	

	○ No important uncertainty or variability	Our systematic review found that the relative importance of the outcomes is as follows: - Pulmonary embolism: 0.63-0.93 (different methods) [1-3] - Deep vein thrombosis: 0.64-0.99 (different methods) [1-5] - Deep vein thrombosis patients' own current health: 0.95 (Time trade off) [3] - Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) [1, 3] - Muscular bleeding: 0.76 (time trade off) [3] - Minor intracranial bleeding event: 0.75 (standard gamble) [1] - Major intracranial bleeding event: 0.15 (standard gamble) [1] - Central nervous system bleeding: 0.29-0.60 (standard gamble) [6, 7]	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		Very low certainty evidence showed small desirable effects and trivial undesirable effects, with possibly important uncertainty or variability in how much people value the outcomes.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies	**The following economic analyses were identified:** Cost of protamine Protamine cost, 1mg: $70.69 USD Cost of clinical events Cost of PE (event cost): $11,616 [8] Cost of recurrent VTE (outpatient, hospitalization, and pharmacy cost in 1-year following VTE event): $11,120 [9]	The cost of protamine administration might be outweighed by the desirable effect on major bleeding.

	○ Don't know	Cost of bleeding: [9] - 6 months following DVT: $11,018 for patients with major bleed - Per-event cost estimated over variable follow-up (mean follow-up = 21.3 months): $22,885 for bleed event requiring hospitalization - Per-event cost: base case treatment of bleeds = $9,935	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies		
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	The panel could not make a judgement as no cost-effectiveness analyses were identified.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced	No research evidence identified.	The panel considered that protamine is on the World Health Organization (WHO) list of essential medicines

	● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		and available in most hospitals. It is unlikely to substantially increase out-of-pocket costs when visiting the ED or when being hospitalized.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence identified.	The panel considered that protamine is being used to reverse major bleeding in patients on LMWH/UFH and is acceptable regarding its effect on bleeding.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	No research evidence identified.	The panel considered that in a life-threatening bleeding situation it may be more difficult to order protamine and to have it prepared and infused, versus a planned surgical procedure. Feasibility might vary according to whether centers perform invasive cardiac procedures or not.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know	
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**	

	JUDGEMENT							IMPLICATIONS
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	

Should temporary cessation of LMWH or UFH plus protamine vs. temporary cessation of LMWH or UFH alone be used be used in patients with LMWH or UFH related life-threatening bleeding during treatment for VTE?

Type of recommendation

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	●	○

Conclusions

RECOMMENDATION	
	The ASH guideline panel suggests using protamine in addition to temporary cessation of LMWH or UFH rather than no protamine in patients with LMWH or UFH related life-threatening bleeding during treatment for VTE (conditional recommendation based on very low certainty in the evidence). Remark: this recommendation does not apply to patients with non-life-threatening bleeding. Although most studies did not specify whether 'heparin' included UFH or LMWH, the panel judged that protamine should primarily be used in patients on UFH.

JUSTIFICATION	The guideline panel determined that there is very low certainty evidence for a net health benefit from using protamine to manage life-threatening bleeding in patients receiving UFH/LMWH therapy for VTE. It is likely that protamine reduces the risk of developing recurrent and/or worsening bleeding and possibly also mortality. The cost of the intervention was deemed negligible and the intervention is unlikely to affect health equity. The intervention is acceptable, but feasibility might vary between settings. Further, the panel felt that this recommendation does not apply to patients with non-life-threatening bleeding.
SUBGROUP CONSIDERATIONS	The panel judged that the intervention should primarily be used in patients on UFH.
IMPLEMENTATION CONSIDERATIONS	Hospitals not performing invasive cardiac procedures should determine whether protamine needs to be made available at their location.
MONITORING AND EVALUATION	No monitoring and evaluation considerations.
RESEARCH PRIORITIES	The panel identified the following additional research priority: Comparative studies assessing the effect of protamine on life-threatening bleeding, in VTE or other patients on UFH/LMWH, as there was only indirect evidence from invasive cardiac procedures identified.

References for Evidence to Decision (EtD) table

1. Hogg K, Kimpton M, Carrier M, Coyle D, Forgie M, Wells P. Estimating quality of life in acute venous thrombosis. JAMA internal medicine. 2013;173(12):1067-72.
2. Hogg K, Shaw J, Coyle D, Fallah P, Carrier M, Wells P. Validity of standard gamble estimated quality of life in acute venous thrombosis. Thrombosis research. 2014;134(4):819-25.
3. Locadia M, Bossuyt PM, Stalmeier PF, Sprangers MA, van Dongen CJ, Middeldorp S, et al. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thrombosis and haemostasis. 2004;92(6):1336-41.
4. Marvig CL, Verhoef TI, de Boer A, Kamali F, Redekop K, Pirmohamed M, et al. Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants. Thrombosis research. 2015;136(1):69-75.
5. Utne KK, Tavoly M, Wik HS, Jelsness-Jorgensen LP, Holst R, Sandset PM, et al. Health-related quality of life after deep vein thrombosis. SpringerPlus. 2016;5(1):1278.
6. Lenert LA, Soetikno RM. Automated computer interviews to elicit utilities: potential applications in the treatment of deep venous thrombosis. Journal of the American Medical Informatics Association : JAMIA. 1997;4(1):49-56.
7. O'Meara JJ, 3rd, McNutt RA, Evans AT, Moore SW, Downs SM. A decision analysis of streptokinase plus heparin as compared with heparin alone for deep-vein thrombosis. The New England journal of medicine. 1994;330(26):1864-9.
8. Saunders RJ, Ozols AA. Cost burden of venous thromboembolism and its prophylaxis in the United States. 2016.
9. Grosse SD, Nelson RE, Nyarko KA, Richardson LC, Raskob GE. The economic burden of incident venous thromboembolism in the United States: A review of estimated attributable healthcare costs. Thromb Res. 2016;137:3-10.

Appendix – Evidence Profile

Q18. In patients with LMWH or UFH related life-threatening bleeding during treatment for VTE should temporary cessation of LMWH or UFH plus protamine vs. temporary cessation of LMWH or UFH alone be used?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	temporary cessation of heparin (LMWH or UFH) plus protamine	temporary cessation of heparin (LMWH or UFH) alone be used	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: mean 30 days)												
6 [1-6]	observational studies	serious [a]	not serious	serious [b]	not serious	none	161/7790 (2.1%)	117/6135 (1.9%)	RR 0.98 (0.66 to 1.45)	**0 fewer per 1,000** (from 6 fewer to 9 more)	⊕◯◯◯ VERY LOW	CRITICAL
PE - Moderate severity - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
DVT in the upper leg - Moderate severity - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	
Thromboembolism (follow up: range 1 days to 30 days; assessed with: Any thromboembolism (stroke or myocardial infarction))												
11 [1-11]	observational studies	serious [a]	not serious	serious [b]	serious [c]	none	154/8915 (1.7%)	181/7967 (2.3%)	RR 0.93 (0.74 to 1.18)	**2 fewer per 1,000** (from 4 more to 6 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Major Bleeding (follow up: range 1 days to 30 days; assessed with: Bleeding requiring re-operation)												
10 [1, 2, 4-6, 8-12]	observational studies	serious [a]	serious [d]	serious [b]	serious [e]	none	210/9579 (2.2%)	233/7134 (3.3%)	RR 0.61 (0.39 to 0.96)	**13 fewer per 1,000** (from 1 fewer to 20 fewer)	⊕◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	temporary cessation of heparin (LMWH or UFH) plus protamine	temporary cessation of heparin (LMWH or UFH) alone be used	Relative (95% CI)	Absolute (95% CI)		
Quality of life impairment - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Duration of hospitalization (assessed with: Duration of hospital stay in hours)												
1 [11]	observational studies	serious [a]	not serious [f]	serious [b]	not serious	none	291	291	-	MD **6.81 lower** (7.73 lower to 5.89 lower)	⨁◯◯◯ VERY LOW	NOT IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Results were not adjusted for potential confounders

b. Protamine indication was cardiovascular surgery and not life-threatening bleeding in VTE patients

c. Lower and upper bounds of the 95% CI for the anticipated absolute effect include important benefit and important harm

d. Non-overlapping confidence intervals and I2=61%

e. Lower and upper bounds of the 95% CI for the anticipated absolute effect include very important benefit and trivial benefit

f. Inconsistency cannot be determined as only one study reported the outcome

References – Included Studies

1. Dellagrammaticas D, Lewis SC, Gough MJ, Collaborators GT. Is heparin reversal with protamine after carotid endarterectomy dangerous? Eur J Vasc Endovasc Surg. 2008;36(1):41-4.
2. McDonald JS, Kallmes DF, Lanzino G, Cloft HJ. Protamine does not increase risk of stroke in patients with elective carotid stenting. Stroke. 2013;44(7):2028-30.
3. Salles LR, Puech-Leao P, Netto BM, Kuzniec S, Aun R, Marino JC, et al. [Risk factors of stroke in carotid endarterectomy]. Rev Hosp Clin Fac Med Sao Paulo. 1997;52(6):291-4.

4. Stone DH, Nolan BW, Schanzer A, Goodney PP, Cambria RA, Likosky DS, et al. Protamine reduces bleeding complications associated with carotid endarterectomy without increasing the risk of stroke. J Vasc Surg. 2010;51(3):559-64, 64 e1.
5. Thuesen L, Andersen HR, Botker HE, Dalby Kristensen S, Krusell LR, Lassen JF. In-laboratory femoral sheath removal after heparin reversal by protamine after percutaneous coronary intervention. EuroIntervention. 2005;1(1):66-9.
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7. Levison JA, Faust GR, Halpern VJ, Theodoris A, Nathan I, Kline RG, et al. Relationship of protamine dosing with postoperative complications of carotid endarterectomy. Ann Vasc Surg. 1999;13(1):67-72.
8. Liu Q, Chen YX, Ni L, Chen Y, Liu CW. [Clinical observation of neutralizing heparin with protamine in carotid endarterectomy]. Zhonghua Yi Xue Za Zhi. 2013;93(33):2650-3.
9. Mauney MC, Buchanan SA, Lawrence WA, Bishop A, Sinclair K, Daniel TM, et al. Stroke rate is markedly reduced after carotid endarterectomy by avoidance of protamine. J Vasc Surg. 1995;22(3):264-9; discussion 9-70.
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11. Rossi ML, Zavalloni D, Scatturin M, Gasparini GL, Lisignoli V, Presbitero P. Immediate removal of femoral-sheath following protamine administration in patients undergoing intracoronary paclitaxel-eluting-stent implantation. Expert Opin Pharmacother. 2007;8(13):2017-24.
12. Morales Gisbert SM, Sala Almonacil VA, Zaragoza Garcia JM, Genoves Gasco B, Gomez Palones FJ, Ortiz Monzon E. Predictors of cervical bleeding after carotid endarterectomy. Annals of Vascular Surgery. 2014;28(2):366-74.

Question #19a

Should a **daily lottery to improve medication adherence** vs. **no daily lottery** be used for **patients receiving anticoagulation therapy for treatment of VTE**?

POPULATION:	patients receiving anticoagulation therapy for treatment of VTE
INTERVENTION:	daily lottery to improve medication adherence
COMPARISON:	no daily lottery
MAIN OUTCOMES:	Mortality; PE - Moderate severity; DVT in the upper leg - Moderate severity; Major bleeding; Quality of life impairment; Time out of therapeutic INR range; Inadequate medication adherence;
SETTING:	Outpatient
PERSPECTIVE:	Clinical recommendation - Population perspective

BACKGROUND: Patients with VTE need to take anticoagulants to treat the VTE and prevent recurrent VTE. As with any medication, patients will need to adhere to the recommended regimen in order to gain maximum benefit from therapy. However, many potential barriers may cause patients to not consistently adhere to their anticoagulant, for example due to minor bleeding events, other side effects, the hassle of injections or INR monitoring, or cost. Interventions specifically designed to improve patient anticoagulant adherence may enhance adherence and optimize patient outcomes. Participation in a daily lottery wherein adherent patients were eligible to receive monetary rewards as an incentive to adhere to anticoagulation is such an intervention.

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Patients with VTE need to take anticoagulants to treat the VTE and prevent recurrent VTE. As with any medication, patients will need to adhere to the recommended regimen in order to gain maximum benefit from therapy. However, many potential barriers may cause patients to not consistently adhere to their anticoagulant, for example due to minor bleeding events, other side effects, the hassle of injections or INR monitoring, or cost. Interventions specifically designed to improve patient anticoagulant adherence may enhance adherence and optimize patient outcomes. Participation in a daily lottery wherein adherent patients were eligible to receive monetary rewards as an incentive to adhere to anticoagulation is such an intervention.	
DESIRABLE	**How substantial are the desirable anticipated effects?** ● Trivial ○ Small	For research evidence on Desirable and Undesirable anticipated effects, as well as the certainty of this evidence, see the **Evidence Profile** in the **Appendix**.	

	○ Moderate ○ Large ○ Varies ○ Don't know		
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ● Large ○ Moderate ○ Small ○ Trivial ○ Varies ○ Don't know		
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies		Very low certainty evidence primarily due to serious risk of bias and very serious imprecision.
VALUES	**Is there important uncertainty about or variability in 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	**Utility related information - the relative importance of outcomes** *Relative importance of the outcomes on a scale 0.00-1.00 with 1.00 indicating a patient comparing the outcome with being in 'Full health' and 0.00 comparing the outcome with being 'Dead'* <u>Our systematic review found that the relative importance of the outcomes is as follows:</u> - Pulmonary embolism: 0.63-0.93 (different methods) [1-3] - Deep vein thrombosis: 0.64-0.99 (different methods) [1-5]	

		- Deep vein thrombosis patients' own current health: 0.95 (Time trade off) [3] - Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) [1, 3] - Muscular bleeding: 0.76 (time trade off) [3] - Minor intracranial bleeding event: 0.75 (standard gamble) [1] - Major intracranial bleeding event: 0.15 (standard gamble) [1] - Central nervous system bleeding: 0.29-0.60 (standard gamble) [6, 7] <u>Our survey among ASH guideline panel members found that the relative importance of QoL and TTR adherence is as follows:</u> - Low time in therapeutic range (TTR): 0.74 [SD 0.25] (ASH panels utility rating) - Inadequate medication adherence: 0.76 (SD 0.26)	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		Very low quality evidence showed trivial desirable effects and large undesirable effects, with possibly important uncertainty or variability in how much people value the outcomes.

RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**The following economic analyses were identified:** <u>Cost of patient self-testing</u> Daily lottery: requires use of an electronic medication monitoring system for each patient, and prizes cost $3 USD per patient per day [8, 9] <u>Cost of clinical events</u> Cost of PE (event cost): $11,616 [10] Cost of recurrent VTE (outpatient, hospitalization, and pharmacy cost in 1-year following VTE event): $11,120 [11] Cost of bleeding: [11] - 6 months following DVT: $11,018 for patients with major bleed - Per-event cost estimated over variable follow-up (mean follow-up = 21.3 months): $22,885 for bleed event requiring hospitalization - Per-event cost: base case treatment of bleeds = $9,935 <u>Cost of medication</u> [12] - Warfarin, per month: $15.84 - $51.50 - DOAC, per month: $300.42 - $600.88 - UFH, per week: $37.00 - LMWH, per week: $199.92 - $712.00	Large costs for applying the intervention, as well as increased clinical event rates.

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ● Low ○ Moderate ○ High ○ No included studies		
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	No research evidence identified.	The panel judged that the intervention will probably not be cost-effective based on the higher risk for adverse events and higher cost with the intervention.
EQUITY	**What would be the impact on health equity?** ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified.	The panel considered that health equity will be reduced if patients have to pay for the electronic medication monitoring system.

ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified.	The panel judged that the intervention will probably not be acceptable; for providers as intervention cost and paying patients to adhere to therapy might not be acceptable; for non-adherent patients as they will also receive a notification that they would have won if they had been adherent.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified.	The panel judged that the intervention is probably not feasible considering the requirement of automated monitoring, patient notifications, payments, and risk of 'gaming' the monitoring system.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	**Large**	Moderate	Small	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies	

	JUDGEMENT							IMPLICATIONS
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies	
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies	
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know	
FEASIBILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know	

Conclusions

Should a daily lottery to improve medication adherence vs. no daily lottery be used in patients receiving anticoagulation therapy for treatment of VTE?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ●	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ○
RECOMMENDATION	The ASH guideline panel suggests not using a daily lottery to improve medication adherence in patients receiving anticoagulation therapy for treatment of VTE (conditional recommendation based on very low certainty in the evidence).				
JUSTIFICATION	The panel made this judgement based on the intervention's unfavorable effects on all critical outcomes, the large costs, and the probable lack of acceptability and feasibility.				
SUBGROUP CONSIDERATIONS	No subgroup considerations.				
IMPLEMENTATION CONSIDERATIONS	No implementation considerations.				
MONITORING AND EVALUATION	No monitoring and evaluation considerations.				
RESEARCH PRIORITIES	The panel identified the following additional research priority: Development and testing of adherence interventions which are acceptable, feasible and affordable. Especially for patients on DOAC, or on VKA and not considered eligible for self-testing or self-management				

References for Evidence to Decision (EtD) table

1. Hogg K, Kimpton M, Carrier M, Coyle D, Forgie M, Wells P. Estimating quality of life in acute venous thrombosis. JAMA internal medicine. 2013;173(12):1067-72.
2. Hogg K, Shaw J, Coyle D, Fallah P, Carrier M, Wells P. Validity of standard gamble estimated quality of life in acute venous thrombosis. Thrombosis research. 2014;134(4):819-25.
3. Locadia M, Bossuyt PM, Stalmeier PF, Sprangers MA, van Dongen CJ, Middeldorp S, et al. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thrombosis and haemostasis. 2004;92(6):1336-41.
4. Marvig CL, Verhoef TI, de Boer A, Kamali F, Redekop K, Pirmohamed M, et al. Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants. Thrombosis research. 2015;136(1):69-75.
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Appendix – Evidence Profile

Q19a. Should a daily lottery to improve medication adherence vs. no daily lottery be used for patients receiving anticoagulation therapy for treatment of VTE?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**daily lottery to improve therapy adherence**	**no daily lottery**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality (follow up: mean 6 months)												
2 [1, 2]	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	1/119 (0.8%)	0/116 (0.0%) [c] 3.9% [c]	RR 2.77 (0.12 to 66.49) [d]	**0 fewer per 1,000** (from 0 fewer to 0 fewer) **69 more per 1,000** (from 34 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL
PE - Moderate severity (follow up: mean 6 months; assessed with: Any TE)												
2 [1, 2]	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	3/116 (2.6%)	0/114 (0.0%) [c] 1.9% [c]	RR 7.22 (0.38 to 136.96) [e]	**0 fewer per 1,000** (from 0 fewer to 0 fewer) **118 more per 1,000** (from 12 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL
DVT in the upper leg - Moderate severity (follow up: mean 6 months; assessed with: Any TE)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**daily lottery to improve therapy adherence**	**no daily lottery**	**Relative (95% CI)**	**Absolute (95% CI)**		
2 [1, 2]	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	3/116 (2.6%)	0/114 (0.0%) [c]	RR 7.22 (0.38 to 136.96) [e]	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
								2.6% [c]		**162 more per 1,000** (from 16 fewer to 1,000 more)		
Major bleeding (follow up: mean 6 months; assessed with: Bleeding associated with hospitalization or ED visit)												
2 [1, 2]	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	7/116 (6.0%)	4/114 (3.5%) [c,f]	RR 1.63 (0.33 to 8.09)	**22 more per 1,000** (from 24 fewer to 249 more)	⊕◯◯◯ VERY LOW	CRITICAL
								1.7% [c,f]		**11 more per 1,000** (from 11 fewer to 121 more)		
								2.1% [c,f]		**13 more per 1,000** (from 14 fewer to 149 more)		
Quality of life impairment - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Time out of therapeutic INR range (follow up: mean 6 months; assessed with: Mean - Kimmel 2012)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	daily lottery to improve therapy adherence	no daily lottery	Relative (95% CI)	Absolute (95% CI)		
2 [1, 2]	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	Kimmel 2016 - Lottery: median 30.1% time INR out of range (IQR: 12.4-46.3); Control: median 31.6% time INR out of range (IQR: 11.1-50.5). OR (fully adjusted model) for likelihood of being out of range with Lottery vs. Control: 0.98 (0.70-1.38). Kimmel 2012 - OR (adjusted for employment status) for likelihood of being out of range with Lottery vs. Control: 0.93 (0.62-1.41).				⊕◯◯◯ VERY LOW	IMPORTANT
Inadequate medication adherence (follow up: mean 6 months)												
2 [1, 2]	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	Kimmel 2016 - Lottery: median 12.1% days with incorrect adherence (IQR: 6.6-25.0); Control: median 23.7% days with incorrect adherence (IQR: 8.1-40.5). Difference (fully adjusted model) for % incorrect adherence with Reminders vs. Control: -7.4% (95% CI: -14.4 - -0.3). Kimmel 2012 - OR (fully adjusted) for likelihood of nonadherence with Lottery vs. Control: 0.84 (0.55-1.28)				⊕◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. No information about treatment allocation concealment, and staff and participants were not blinded

b. Lower and upper bounds of the 95% CI for the anticipated absolute effect include important benefit and important harm

c. Median annual risk among 11 RCTs comparing LMWH/VKA with DOAC in patients requiring treatment for VTE.[3-13] This risk was observed in the original trial at 6 months and to obtain the annual risk, we assumed a linear increase over time and doubled the risk observed at 6 months. See also the ASH guideline on Treatment of VTE

d. Kimmel 2016 had 0 deaths in both treatment groups and was not used to calculate the RR.

e. Kimmel 2012 had 0 thromboembolic events in both treatment groups and was not used to calculate the RR.

f. High bleeding risk of 2.1% in patients treated with anticoagulants for 6 months, from a systematic review of 13 prospective cohort studies and 56 randomized trials.[14] See also the ASH guideline on Treatment of VTE

References – Included RCTs

1. Kimmel SE, Troxel AB, French B, Loewenstein G, Doshi JA, Hecht TE, et al. A randomized trial of lottery-based incentives and reminders to improve warfarin adherence: the Warfarin Incentives (WIN2) Trial. Pharmacoepidemiol Drug Saf. 2016;25(11):1219-27.
2. Kimmel SE, Troxel AB, Loewenstein G, Brensinger CM, Jaskowiak J, Doshi JA, et al. Randomized trial of lottery-based incentives to improve warfarin adherence. Am Heart J. 2012;164(2):268-7**References –Studies for Baseline Risk**
3. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med. 2013;369(9):799-808.
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Question #19b

Should **electronic reminders to improve medication adherence** vs. **no electronic reminders** be used for **patients receiving anticoagulation therapy for treatment of VTE**?

POPULATION:	patients receiving anticoagulation therapy for treatment of VTE
INTERVENTION:	electronic reminders to improve medication adherence
COMPARISON:	no electronic reminders
MAIN OUTCOMES:	Mortality; PE - Moderate severity; DVT in the upper leg - Moderate severity; Major bleeding; Quality of life impairment; Time out of therapeutic INR range; Inadequate medication adherence;
SETTING:	Outpatient
PERSPECTIVE:	Clinical recommendation - Population perspective

BACKGROUND: Patients with VTE need to take anticoagulants to treat the VTE and prevent recurrent VTE. As with any medication, patients will need to adhere to the recommended regimen in order to gain maximum benefit from therapy. However, many potential barriers may cause patients to not consistently adhere to their anticoagulant, for example due to minor bleeding events, other side effects, the hassle of injections or INR monitoring, or cost. Interventions specifically designed to improve patient anticoagulant adherence may enhance adherence and optimize patient outcomes. Receiving daily electronic reminders to take medications is such an intervention.

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Patients with VTE need to take anticoagulants to treat the VTE and prevent recurrent VTE. As with any medication, patients will need to adhere to the recommended regimen in order to gain maximum benefit from therapy. However, many potential barriers may cause patients to not consistently adhere to their anticoagulant, for example due to minor bleeding events, other side effects, the hassle of injections or INR monitoring, or cost. Interventions specifically designed to improve patient anticoagulant adherence may enhance adherence and optimize patient outcomes. Receiving daily electronic reminders to take medications is such an intervention.	
DESIRABLE	**How substantial are the desirable anticipated effects?** ● Trivial ○ Small	For research evidence on Desirable and Undesirable anticipated effects, as well as the certainty of this evidence, see the **Evidence Profile** in the **Appendix**.	

	○ Moderate ○ Large ○ Varies ○ Don't know		
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know		
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies		Very low certainty evidence primarily due to serious risk of bias and very serious imprecision.
VALUES	**Is there important uncertainty about or variability in 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	**Utility related information - the relative importance of outcomes** *Relative importance of the outcomes on a scale 0.00-1.00 with 1.00 indicating a patient comparing the outcome with being in 'Full health' and 0.00 comparing the outcome with being 'Dead'* <u>Our systematic review found that the relative importance of the outcomes is as follows:</u> - Pulmonary embolism: 0.63-0.93 (different methods) [1-3] - Deep vein thrombosis: 0.64-0.99 (different methods) [1-5]	

		- Deep vein thrombosis patients' own current health: 0.95 (Time trade off) [3] - Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) [1, 3] - Muscular bleeding: 0.76 (time trade off) [3] - Minor intracranial bleeding event: 0.75 (standard gamble) [1] - Major intracranial bleeding event: 0.15 (standard gamble) [1] - Central nervous system bleeding: 0.29-0.60 (standard gamble) [6, 7] <u>Our survey among ASH guideline panel members found that the relative importance of TTR and medication adherence is as follows:</u> - Low time in therapeutic range (TTR): 0.74 [SD 0.25] (ASH panels utility rating) - Inadequate medication adherence: 0.76 (SD 0.26)	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know		The panel could not make a judgement as only one small RCT was included, showing a trivial effect on TTR, no effect on major bleeding, and unknown effect on all other critical outcomes.

RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**The following economic analyses were identified:** <u>Cost of electronic reminders</u> Electronic reminders: requires use of an electronic medication monitoring system for each patient [8, 9] <u>Cost of clinical events</u> Cost of PE (event cost): $11,616 [10] Cost of recurrent VTE (outpatient, hospitalization, and pharmacy cost in 1-year following VTE event): $11,120 [11] Cost of bleeding: [11] - 6 months following DVT: $11,018 for patients with major bleed - Per-event cost estimated over variable follow-up (mean follow-up = 21.3 months): $22,885 for bleed event requiring hospitalization - Per-event cost: base case treatment of bleeds = $9,935 <u>Cost of medications</u> [12] - Warfarin, per month: $15.84 - $51.50 - DOAC, per month: $300.42 - $600.88 - UFH, per week: $37.00 - LMWH, per week: $199.92 - $712.00	Large costs for applying the intervention, if reminders are delivered using an automated system.
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ● Low ○ Moderate ○ High ○ No included studies		

COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	The panel could not provide a judgement as no cost-effectiveness studies were identified and the effects of the intervention are uncertain.
EQUITY	**What would be the impact on health equity?** ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified.	The panel considered that health equity will be reduced if patients have to pay for the electronic medication monitoring system.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	No research evidence identified.	The panel judged that acceptability of the intervention will probably vary, depending on who is paying for the intervention and how accepting patients and providers are of the electronic medication monitoring system.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified.	The panel judged that the intervention is probably not feasible as many patients will likely not have access to the electronic medication monitoring system needed to send automated reminders.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**	
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**	
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**	

	JUDGEMENT							IMPLICATIONS
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	
FEASIBILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know	

Conclusions

Should electronic reminders to improve medication adherence vs. no electronic reminders be used in patients receiving anticoagulation therapy for treatment of VTE?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ●	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ○
RECOMMENDATION	The ASH guideline panel suggests not using electronic reminders to improve medication adherence in patients receiving anticoagulation therapy for treatment of VTE (conditional recommendation based on very low certainty in the evidence).				
JUSTIFICATION	The panel made this judgement based on very low certainty evidence showing the intervention's uncertain effects, the large costs, and the probable lack of feasibility.				
SUBGROUP CONSIDERATIONS	No subgroup considerations.				
IMPLEMENTATION CONSIDERATIONS	No implementation considerations.				
MONITORING AND EVALUATION	No monitoring and evaluation considerations.				

RESEARCH PRIORITIES	The panel identified the following additional research priority: Development and testing of adherence interventions which are acceptable, feasible and affordable. Especially for patients on DOAC, or on VKA and not considered eligible for self-testing or self-management

References for Evidence to Decision (EtD) table

1. Hogg K, Kimpton M, Carrier M, Coyle D, Forgie M, Wells P. Estimating quality of life in acute venous thrombosis. JAMA internal medicine. 2013;173(12):1067-72.
2. Hogg K, Shaw J, Coyle D, Fallah P, Carrier M, Wells P. Validity of standard gamble estimated quality of life in acute venous thrombosis. Thrombosis research. 2014;134(4):819-25.
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4. Marvig CL, Verhoef TI, de Boer A, Kamali F, Redekop K, Pirmohamed M, et al. Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants. Thrombosis research. 2015;136(1):69-75.
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Appendix – Evidence Profile

Q19b. Should electronic reminders to improve medication adherence vs. no electronic reminders be used for patients receiving anticoagulation therapy for treatment of VTE?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	electronic reminders to improve therapy adherence	no electronic reminders	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: mean 6 months)												
1 [1]	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	0/67 (0.0%)	0/66 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	CRITICAL
PE - Moderate severity (follow up: mean 6 months; assessed with: Any TE)												
1 [1]	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	0/67 (0.0%)	0/66 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	CRITICAL
DVT in the upper leg - Moderate severity (follow up: mean 6 months; assessed with: Any TE)												
1 [1]	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	0/67 (0.0%)	0/66 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	CRITICAL
Major bleeding (follow up: mean 6 months; assessed with: Bleeding associated with hospitalization or ED visit)												
1 [1]	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	4/64 (6.3%)	4/65 (6.2%) [d,e] 1.7% [d,e]	RR 1.02 (0.27 to 3.89)	**1 more per 1,000** (from 45 fewer to 178 more) **0 fewer per 1,000** (from 12 fewer to 49 more)	⨁◯◯◯ VERY LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**electronic reminders to improve therapy adherence**	**no electronic reminders**	**Relative (95% CI)**	**Absolute (95% CI)**		
								2.1% [d,e]		**0 fewer per 1,000** (from 15 fewer to 61 more)		
Quality of life impairment - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Time out of therapeutic INR range (follow up: mean 6 months)												
1 [1]	randomised trials	serious [a]	not serious	not serious	very serious [f]	none	Electronic reminders: median 23.8% time INR out of range (IQR: 8.8-36.6); Control: median 31.6% time INR out of range (IQR: 11.1-50.5). OR (fully adjusted model) for likelihood of being out of range with Electronic reminders vs. Control: 0.64 (0.45-0.93)				⊕◯◯◯ VERY LOW	IMPORTANT
Inadequate medication adherence (follow up: mean 6 months)												
1 [1]	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	Electronic reminders: median 21.8% days with incorrect adherence (IQR: 6.9-39.5); Control: median 23.7% days with incorrect adherence (IQR: 8.1-40.5). Difference (fully adjusted model) for % incorrect adherence with Electronic reminders vs. Control: -2.0% (95% CI: -8.2 - 4.2)				⊕◯◯◯ VERY LOW	IMPORTANT

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

Explanations

a. No information about treatment allocation concealment, and staff and participants were not blinded

b. Very small sample size, no events in both treatment groups

c. Lower and upper bounds of the 95% CI for the anticipated absolute effect include important benefit and important harm

d. Median annual risk among 11 RCTs comparing LMWH/VKA with DOAC in patients requiring treatment for VTE.[2-12] This risk was observed in the original trial at 6 months and to obtain the annual risk, we assumed a linear increase over time and doubled the risk observed at 6 months. See also the ASH guideline on Treatment of VTE

e. High bleeding risk of 2.1% in patients treated with anticoagulants for 6 months, from a systematic review of 13 prospective cohort studies and 56 randomized trials.[13] See also the ASH guideline on Treatment of VTE

f. Lower and upper bounds of the 95% CI for the anticipated absolute effect include highly important benefit and a small benefit

References – Included RCTs

1. Kimmel SE, Troxel AB, French B, Loewenstein G, Doshi JA, Hecht TE, et al. A randomized trial of lottery-based incentives and reminders to improve warfarin adherence: the Warfarin Incentives (WIN2) Trial. Pharmacoepidemiol Drug Saf. 2016;25(11):1219-27.

References –Studies for Baseline Risk

2. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med. 2013;369(9):799-808.
3. Agnelli G, Gallus A, Goldhaber SZ, Haas S, Huisman MV, Hull RD, et al. Treatment of proximal deep-vein thrombosis with the oral direct factor Xa inhibitor rivaroxaban (BAY 59-7939): the ODIXa-DVT (Oral Direct Factor Xa Inhibitor BAY 59-7939 in Patients With Acute Symptomatic Deep-Vein Thrombosis) study. Circulation. 2007;116(2):180-7.
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Question #19c

Should a **daily lottery plus electronic reminders to improve medication adherence** vs. **no daily lottery or electronic reminders** be used for **patients receiving anticoagulation therapy for treatment of VTE**?

POPULATION:	patients receiving anticoagulation therapy for treatment of VTE
INTERVENTION:	daily lottery plus electronic reminders to improve medication adherence
COMPARISON:	no daily lottery or electronic reminders
MAIN OUTCOMES:	Mortality; PE - Moderate severity; DVT in the upper leg - Moderate severity; Major bleeding; Quality of life impairment; Time out of therapeutic INR range; Inadequate medication adherence;
SETTING:	Outpatient
PERSPECTIVE:	Clinical recommendation - Population perspective

BACKGROUND: Patients with VTE need to take anticoagulants to treat the VTE and prevent recurrent VTE. As with any medication, patients will need to adhere to the recommended regimen in order to gain maximum benefit from therapy. However, many potential barriers may cause patients to not consistently adhere to their anticoagulant, for example due to minor bleeding events, other side effects, the hassle of injections or INR monitoring, or cost. Interventions specifically designed to improve patient anticoagulant adherence may enhance adherence and optimize patient outcomes. Participation in a daily lottery wherein adherent patients were eligible to receive monetary rewards as an incentive to adhere to anticoagulation and receiving daily electronic reminders to take medications are such interventions.

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Patients with VTE need to take anticoagulants to treat the VTE and prevent recurrent VTE. As with any medication, patients will need to adhere to the recommended regimen in order to gain maximum benefit from therapy. However, many potential barriers may cause patients to not consistently adhere to their anticoagulant, for example due to minor bleeding events, other side effects, the hassle of injections or INR monitoring, or cost. Interventions specifically designed to improve patient anticoagulant adherence may enhance adherence and optimize patient outcomes. Participation in a daily lottery wherein adherent patients were eligible to receive monetary rewards as an incentive to adhere to anticoagulation and receiving daily electronic reminders to take medications are such interventions.	

DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	For research evidence on Desirable and Undesirable anticipated effects, as well as the certainty of this evidence, see the **Evidence Profile** in the **Appendix**.	
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies		Very low certainty evidence primarily due to serious risk of bias and very serious imprecision.
VALUES	**Is there important uncertainty about or variability in 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	**Utility related information - the relative importance of outcomes** *Relative importance of the outcomes on a scale 0.00-1.00 with 1.00 indicating a patient comparing the outcome with being in 'Full health' and 0.00 comparing the outcome with being 'Dead'* <u>Our systematic review found that the relative importance of the outcomes is as follows:</u>	

		- Pulmonary embolism: 0.63-0.93 (different methods) [1-3] - Deep vein thrombosis: 0.64-0.99 (different methods) [1-5] - Deep vein thrombosis patients' own current health: 0.95 (Time trade off) [3] - Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) [1, 3] - Muscular bleeding: 0.76 (time trade off) [3] - Minor intracranial bleeding event: 0.75 (standard gamble) [1] - Major intracranial bleeding event: 0.15 (standard gamble) [1] - Central nervous system bleeding: 0.29-0.60 (standard gamble) [6, 7] <u>Our survey among ASH guideline panel members found that the relative importance of TTR and medication adherence is as follows:</u> - Low time in therapeutic range (TTR): 0.74 [SD 0.25] (ASH panels utility rating) - Inadequate medication adherence: 0.76 (SD 0.26)	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know		The panel could not make a judgement as only one small RCT was included, showing trivial effects on major bleeding, TTR and therapy adherence, and unknown effect on all other critical outcomes.

RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**The following economic analyses were identified:** <u>Cost of daily lottery + electronic reminders</u> Daily lottery: requires use of an electronic medication monitoring system for each patient, and prizes cost $3 USD per patient per day [8, 9] Electronic reminders: requires use of an electronic medication monitoring system for each patient [8, 9] <u>Cost of clinical events</u> Cost of PE (event cost): $11,616 [10] Cost of recurrent VTE (outpatient, hospitalization, and pharmacy cost in 1-year following VTE event): $11,120 [11] Cost of bleeding: [11] - 6 months following DVT: $11,018 for patients with major bleed - Per-event cost estimated over variable follow-up (mean follow-up = 21.3 months): $22,885 for bleed event requiring hospitalization - Per-event cost: base case treatment of bleeds = $9,935 <u>Cost of medication</u> [12] - Warfarin, per month: $15.84 - $51.50 - DOAC, per month: $300.42 - $600.88 - UFH, per week: $37.00 - LMWH, per week: $199.92 - $712.00	Large costs for applying the intervention when using the automated electronic monitoring system.

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ● Low ○ Moderate ○ High ○ No included studies		
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	The panel could not provide a judgement as no cost-effectiveness studies were identified and the effects of the intervention are uncertain.
EQUITY	**What would be the impact on health equity?** ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified.	The panel considered that health equity will be reduced if patients have to pay for the electronic medication monitoring system.

ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified.	The panel judged that the intervention will probably not be acceptable; for providers as intervention cost and paying patients to adhere to therapy might not be acceptable; for non-adherent patients as they will also receive a notification that they would have won if they had been adherent.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified.	The panel judged that the intervention is probably not feasible considering the requirement of automated monitoring, patient notifications, payments, and risk of 'gaming' the monitoring system.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know	
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies	

	JUDGEMENT							IMPLICATIONS
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**	
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**	
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know	
FEASIBILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know	

Conclusions

Should a daily lottery plus electronic reminders to improve medication adherence vs. no daily lottery or electronic reminders be used in patients receiving anticoagulation therapy for treatment of VTE?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention ●	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ○
RECOMMENDATION	The ASH guideline panel recommends not using a daily lottery plus electronic reminders to improve medication adherence in patients receiving anticoagulation therapy for treatment of VTE (strong recommendation based on very low certainty in the evidence).				
JUSTIFICATION	The panel decided on a strong recommendation against the intervention based on very low quality evidence pointing towards harm for all critical outcomes, and the intervention having large costs and not being acceptable nor feasible.				
SUBGROUP CONSIDERATIONS	No subgroup considerations.				
IMPLEMENTATION CONSIDERATIONS	No implementation considerations.				
MONITORING AND EVALUATION	No monitoring and evaluation considerations.				
RESEARCH PRIORITIES	The panel identified the following additional research priority: Development and testing of adherence interventions which are acceptable, feasible and affordable. Especially for patients on DOAC, or on VKA and not considered eligible for self-testing or self-management				

References for Evidence to Decision (EtD) table

1. Hogg K, Kimpton M, Carrier M, Coyle D, Forgie M, Wells P. Estimating quality of life in acute venous thrombosis. JAMA internal medicine. 2013;173(12):1067-72.
2. Hogg K, Shaw J, Coyle D, Fallah P, Carrier M, Wells P. Validity of standard gamble estimated quality of life in acute venous thrombosis. Thrombosis research. 2014;134(4):819-25.
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8. Kimmel SE, Troxel AB, French B, Loewenstein G, Doshi JA, Hecht TE, et al. A randomized trial of lottery-based incentives and reminders to improve warfarin adherence: the Warfarin Incentives (WIN2) Trial. Pharmacoepidemiol Drug Saf. 2016;25(11):1219-27.
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11. Grosse SD, Nelson RE, Nyarko KA, Richardson LC, Raskob GE. The economic burden of incident venous thromboembolism in the United States: A review of estimated attributable healthcare costs. Thromb Res. 2016;137:3-10.
12. Biskupiak J, Ghate SR, Jiao T, Brixner D. Cost implications of formulary decisions on oral anticoagulants in nonvalvular atrial fibrillation. Journal of managed care pharmacy : JMCP. 2013;19(9):789-98.

Appendix – Evidence Profile

Q19c. Should a daily lottery plus electronic reminders to improve medication adherence vs. no daily lottery or electronic reminders be used for patients receiving anticoagulation therapy for treatment of VTE?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	daily lottery plus electronic reminders to improve therapy adherence	no daily lottery or electronic reminders	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: mean 6 months)												
1 [1]	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	0/68 (0.0%)	0/66 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	CRITICAL
PE - Moderate severity (follow up: mean 6 months; assessed with: Any TE)												
1 [1]	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	0/68 (0.0%)	0/66 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	CRITICAL
DVT in the upper leg - Moderate severity (follow up: mean 6 months; assessed with: Any TE)												
1 [1]	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	0/68 (0.0%)	0/66 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	CRITICAL
Major bleeding (follow up: mean 6 months; assessed with: Bleeding associated with hospitalization or ED visit)												
1 [1]	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	5/66 (7.6%)	4/65 (6.2%) [d,e]	RR 1.23 (0.35 to 4.38)	**14 more per 1,000** (from 40 fewer to 208 more)	⨁◯◯◯ VERY LOW	CRITICAL
								1.7% [d,e]		**4 more per 1,000** (from 11 fewer to 57 more)		
								2.1% [d,e]		**5 more per 1,000** (from 14 fewer to 71 more)		

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	daily lottery plus electronic reminders to improve therapy adherence	no daily lottery or electronic reminders	Relative (95% CI)	Absolute (95% CI)		
Quality of life impairment - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Time out of therapeutic INR range (follow up: mean 6 months)												
1 [1]	randomised trials	serious [a]	not serious	not serious	very serious [c]	none	Lottery + Reminders: median 23.9% time INR out of range (IQR: 9.9-42.7); Control: median 31.6% time INR out of range (IQR: 11.1-50.5). OR (fully adjusted model) for likelihood of being out of range with Reminders vs. Control: 0.77 (0.54-1.09)				⨁◯◯◯ VERY LOW	
Inadequate medication adherence (follow up: mean 6 months)												
1 [1]	randomised trials	serious [a]	not serious	not serious	very serious [c,f]	none	Lottery + Reminders: median 17.6% days with incorrect adherence (IQR: 7.0-43.6); Control: median 23.7% days with incorrect adherence (IQR: 8.1-40.5). Difference (fully adjusted model) for % incorrect adherence with Reminders vs. Control: -4.6% (95% CI: -11.1 - 1.9)				⨁◯◯◯ VERY LOW	CRITICAL

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

Explanations

a. No information about treatment allocation concealment, and staff and participants were not blinded

b. Very small sample size, no events in both treatment groups

c. Lower and upper bounds of the 95% CI for the anticipated absolute effect include important benefit and important harm

d. Median annual risk among 11 RCTs comparing LMWH/VKA with DOAC in patients requiring treatment for VTE.[2-12] This risk was observed in the original trial at 6 months and to obtain the annual risk, we assumed a linear increase over time and doubled the risk observed at 6 months. See also the ASH guideline on Treatment of VTE

e. High bleeding risk of 2.1% in patients treated with anticoagulants for 6 months, from a systematic review of 13 prospective cohort studies and 56 randomized trials.[13] See also the ASH guideline on Treatment of VTE

f. Lower and upper bounds of the 95% CI for the anticipated absolute effect include important benefit and some harm

References – Included RCTs

1. Kimmel SE, Troxel AB, French B, Loewenstein G, Doshi JA, Hecht TE, et al. A randomized trial of lottery-based incentives and reminders to improve warfarin adherence: the Warfarin Incentives (WIN2) Trial. Pharmacoepidemiol Drug Saf. 2016;25(11):1219-27.

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Question #19d

Should a **visual medication schedule to improve medication adherence** vs. **no visual medication schedule** be used for **patients receiving anticoagulation therapy for treatment of VTE**?

POPULATION:	patients receiving anticoagulation therapy for treatment of VTE
INTERVENTION:	visual medication schedule to improve medication adherence
COMPARISON:	no visual medication schedule
MAIN OUTCOMES:	Mortality; PE - Moderate severity; DVT in the upper leg - Moderate severity; Major bleeding; Quality of life impairment; Time in therapeutic INR range; Inadequate medication adherence; Hospitalization;
SETTING:	Outpatient
PERSPECTIVE:	Clinical recommendation - Population perspective

BACKGROUND: Patients with VTE need to take anticoagulants to treat the VTE and prevent recurrent VTE. As with any medication, patients will need to adhere to the recommended regimen in order to gain maximum benefit from therapy. However, many potential barriers may cause patients to not consistently adhere to their anticoagulant, for example due to minor bleeding events, other side effects, the hassle of injections or INR monitoring, or cost. Interventions specifically designed to improve patient anticoagulant adherence may enhance adherence and optimize patient outcomes. The use of a visual medication schedule wherein medications and administration times are represented graphically is such an intervention.

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Patients with VTE need to take anticoagulants to treat the VTE and prevent recurrent VTE. As with any medication, patients will need to adhere to the recommended regimen in order to gain maximum benefit from therapy. However, many potential barriers may cause patients to not consistently adhere to their anticoagulant, for example due to minor bleeding events, other side effects, the hassle of injections or INR monitoring, or cost. Interventions specifically designed to improve patient anticoagulant adherence may enhance adherence and optimize patient outcomes. The use of a visual medication schedule wherein medications and administration times are represented graphically is such an intervention.	

DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	For research evidence on Desirable and Undesirable anticipated effects, as well as the certainty of this evidence, see the **Evidence Profile** in the **Appendix.**	
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know		
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies		Very low certainty evidence primarily due to serious risk of bias and very serious imprecision.
VALUES	**Is there important uncertainty about or variability in 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	**Utility related information - the relative importance of outcomes** *Relative importance of the outcomes on a scale 0.00-1.00 with 1.00 indicating a patient comparing the outcome with being in 'Full health' and 0.00 comparing the outcome with being 'Dead'* <u>Our systematic review found that the relative importance of the outcomes is as follows:</u>	

		- Pulmonary embolism: 0.63-0.93 (different methods) [1-3] - Deep vein thrombosis: 0.64-0.99 (different methods) [1-5] - Deep vein thrombosis patients' own current health: 0.95 (Time trade off) [3] - Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) [1, 3] - Muscular bleeding: 0.76 (time trade off) [3] - Minor intracranial bleeding event: 0.75 (standard gamble) [1] - Major intracranial bleeding event: 0.15 (standard gamble) [1] - Central nervous system bleeding: 0.29-0.60 (standard gamble) [6, 7] <u>Our survey among ASH guideline panel members found that the relative importance of TTR and medication adherence is as follows:</u> - Low time in therapeutic range (TTR): 0.74 [SD 0.25] (ASH panels utility rating) - Inadequate medication adherence: 0.76 (SD 0.26)	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know		The panel could not make a judgement as only one small RCT was included, showing trivial effect on TTR and uncertain effects on critical outcomes.

RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**The following economic analyses were identified:** <u>Cost of clinical events</u> Cost of PE (event cost): $11,616 [8] Cost of recurrent VTE (outpatient, hospitalization, and pharmacy cost in 1-year following VTE event): $11,120 [9] Cost of bleeding: [9] - 6 months following DVT: $11,018 for patients with major bleed - Per-event cost estimated over variable follow-up (mean follow-up = 21.3 months): $22,885 for bleed event requiring hospitalization - Per-event cost: base case treatment of bleeds = $9,935 <u>Cost of medication</u> [10] - Warfarin, per month: $15.84 - $51.50 - DOAC, per month: $300.42 - $600.88 - UFH, per week: $37.00 - LMWH, per week: $199.92 - $712.00	The panel judged that there will be moderate costs for generating & printing visual medication schedules, and brief counseling.
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ● Low ○ Moderate ○ High ○ No included studies		

COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	The panel could not provide a judgement as no cost-effectiveness studies were identified and the effects of the intervention are uncertain.
EQUITY	**What would be the impact on health equity?** ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified.	The panel considered that the health equity for patients with poor health literacy and/or visual impairments might be reduced.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified.	The panel judged that the intervention is probably acceptable; for providers if counseling time is kept to a minimum, or as part of usual counseling; for patients there are not clear downsides.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence identified.	The panel considered that visual schedules are being used in some settings, with or without counseling.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**	
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**	
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**	

	JUDGEMENT							IMPLICATIONS
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know	

Conclusions

Should a visual medication schedule to improve medication adherence vs. no visual medication schedule be used in patients receiving anticoagulation therapy for treatment of VTE?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	●	○	○	○
RECOMMENDATION	The ASH guideline panel suggests not using visual medication schedules to improve medication adherence in patients receiving anticoagulation therapy for treatment of VTE (conditional recommendation based on very low certainty in the evidence).				
JUSTIFICATION	The panel made this judgement based on very low certainty evidence showing the intervention's uncertain effects, the moderate costs, and the possible reduction in health equity.				
SUBGROUP CONSIDERATIONS	No subgroup considerations.				
IMPLEMENTATION CONSIDERATIONS	No implementation considerations.				
MONITORING AND EVALUATION	No monitoring and evaluation considerations.				

RESEARCH PRIORITIES	The panel identified the following additional research priority: Development and testing of adherence interventions which are acceptable, feasible and affordable. Especially for patients on DOAC, or on VKA and not considered eligible for self-testing or self-management

References for Evidence to Decision (EtD) table

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Appendix – Evidence Profile

Q19d. Should a visual medication schedule to improve medication adherence vs. no visual medication schedule be used for patients receiving anticoagulation therapy for treatment of VTE?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	visual medication schedule to improve therapy adherence	no visual medication schedule	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: mean 6 months)												
1 [1]	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	1/74 (1.4%)	0/73 (0.0%) [c]	RR 2.96 (0.12 to 71.50)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
								3.9% [c]		**76 more per 1,000** (from 34 fewer to 1,000 more)		
PE - Moderate severity (follow up: mean 6 months; assessed with: Any thromboembolism)												
1 [1]	randomised trials	serious [a]	not serious	not serious	very serious [d]	none	0/74 (0.0%)	0/73 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	CRITICAL
DVT in the upper leg - Moderate severity (follow up: mean 6 months; assessed with: Any thromboembolism)												
1 [1]	randomised trials	serious [a]	not serious	not serious	very serious [d]	none	0/74 (0.0%)	0/73 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	CRITICAL
Major bleeding - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Quality of life impairment - not reported												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	visual medication schedule to improve therapy adherence	no visual medication schedule	Relative (95% CI)	Absolute (95% CI)		
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Time in therapeutic INR range (follow up: mean 6 months; Scale from: 0 to 100)												
1 [1]	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	74	73	-	MD 2.6 % higher (7.6 lower to 12.9 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Inadequate medication adherence - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Hospitalization (assessed with: any hospitalization, not related to anticoagulation use or indication)												
1 [1]	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	10/74 (13.5%)	2/73 (2.7%)	RR 4.93 (1.12 to 21.74)	**108 more per 1,000** (from 3 more to 568 more)	⨁◯◯◯ VERY LOW	NOT IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Staff and participants were not blinded, and both groups receiving standard medication counseling and anticoagulation clinic follow-up.

b. Lower and upper bounds of the 95% CI for the anticipated absolute effect include important benefit and important harm

c. Median annual risk among 11 RCTs comparing LMWH/VKA with DOAC in patients requiring treatment for VTE.[2-12] This risk was observed in the original trial at 6 months and to obtain the annual risk, we assumed a linear increase over time and doubled the risk observed at 6 months. See also the ASH guideline on Treatment of VTE

d. Very small sample size, no events in both treatment groups

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Question #20

Should **measurement of the DOAC anticoagulant effect** vs. **no measurement of the DOAC anticoagulant effect** be used **during management of DOAC-related bleeding in patients receiving DOAC therapy for the treatment of VTE**?

POPULATION:	bleeding in patients receiving DOAC therapy for the treatment of VTE
INTERVENTION:	measurement of the DOAC anticoagulant effect
COMPARISON:	no measurement of the DOAC anticoagulant effect
MAIN OUTCOMES:	Mortality; PE - Moderate severity; DVT in the upper leg - Moderate severity; Major bleeding; Quality of life impairment; Delay of intervention;
SETTING:	Inpatient
PERSPECTIVE:	Clinical recommendation - Population perspective

BACKGROUND: Patients with venous thromboembolism (VTE) using direct oral anticoagulants (DOACs) are at risk of bleeding. While DOACs have generally been considered to not require routine laboratory monitoring, acute bleeding represents one situation where such monitoring may be warranted. DOACs are often discontinued in such a setting, but additional laboratory monitoring of anticoagulant effect levels at presentation might reveal if the bleeding is indeed due to an elevated DOAC level. If so, a reversal agent can be administered to more rapidly reverse the bleeding and prevent serious events such as prolonged bleeds, re-bleeds and fatality. Additional laboratory measurements may reveal whether a reversal strategy has successfully eliminated the DOAC's anticoagulant effect.

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Patients with venous thromboembolism (VTE) using direct oral anticoagulants (DOACs) are at risk of bleeding. While DOACs have generally been considered to not require routine laboratory monitoring, acute bleeding represents one situation where such monitoring may be warranted. DOACs are often discontinued in such a setting, but additional laboratory monitoring of anticoagulant effect levels at presentation might reveal if the bleeding is indeed due to an elevated DOAC level. If so, a reversal agent can be administered to more rapidly reverse the bleeding and prevent serious events such as prolonged bleeds, re-bleeds and fatality. Additional laboratory measurements may reveal whether a reversal strategy has successfully eliminated the DOAC's anticoagulant effect.	

DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	For research evidence on Desirable and Undesirable anticipated effects, as well as the certainty of this evidence, see the **Evidence Profile** in the **Appendix**.	The panel could not make a judgement in the absence of a direct comparison, as well as the absence of standardized DOAC tests.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know		The panel could not make a judgement in the absence of a direct comparison, as well as the absence of standardized DOAC tests.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies		Very low certainty evidence primarily due to very serious indirectness as the indirect comparison for mortality was based on studies only reporting intervention or control, and other critical outcomes lacked comparisons.
VALUES	**Is there important uncertainty about or variability in 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	**Utility related information - the relative importance of outcomes** *Relative importance of the outcomes on a scale 0.00-1.00 with 1.00 indicating a patient comparing the outcome with being in 'Full health' and 0.00 comparing the outcome with being 'Dead'* <u>Our systematic review found that the relative importance of the outcomes is as follows:</u>	

		- Pulmonary embolism: 0.63-0.93 (different methods) [1-3] - Deep vein thrombosis: 0.64-0.99 (different methods) [1-5] - Deep vein thrombosis patients' own current health: 0.95 (Time trade off) [3] - Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) [1, 3] - Muscular bleeding: 0.76 (time trade off) [3] - Minor intracranial bleeding event: 0.75 (standard gamble) [1] - Major intracranial bleeding event: 0.15 (standard gamble) [1] - Central nervous system bleeding: 0.29-0.60 (standard gamble) [6, 7]	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know	Effect estimate could be provided for only one critical outcome (Mortality) and the very low quality of the evidence (primarily due to the indirectness regarding population, intervention and comparisons) makes it highly uncertain what the balance of the desirable and undesirable effects is.	The panel could not make a judgement due to the very low certainty evidence and unknown effects.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know	**The following economic analyses were identified:** <u>Cost of laboratory tests</u> Laboratory test costs (USD) (University of Nevada Las Vegas Quest Diagnostics Vendor Fee Schedule, 2016): - CBC with differential: $12.67 - PT (Prothrombin Time) + INR: $3.22 - PTT (Partial Thromboplastin Time): $6.30 - TT (Thrombin Time): $26.25 - Factor X Activity: $53.20	The panel could not make a judgement as the use of monitoring assays may increase costs, but could lead to cost savings if the DOAC is absent and no reversal agent is needed.

		Cost of clinical events Cost of PE (event cost): $11,616 [8] Cost of recurrent VTE (outpatient, hospitalization, and pharmacy cost in 1-year following VTE event): $11,120 [9] Cost of bleeding: [9] - 6 months following DVT: $11,018 for patients with major bleed - Per-event cost estimated over variable follow-up (mean follow-up = 21.3 months): $22,885 for bleed event requiring hospitalization - Per-event cost: base case treatment of bleeds = $9,935 Cost of medication [10] - DOAC, per month: $300.42 - $600.88	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies		

COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	The panel could not make a judgement as no cost-effectiveness studies were identified, and it is unknown if there is a difference in cost and whether a higher cost would be offset by fewer clinical events.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified.	The panel judged that if a specific DOAC test would be available in hospitals, all bleeding patients coming in would receive the test. It is possible that a test might not be available in all hospitals.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified.	Anticoagulation monitoring tests are acceptable as they are currently being used, but it is uncertain if the wait time to receive the result is acceptable in patients with a major bleeding.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	No research evidence identified.	The panel judged that the intervention is probably feasible if a validated test is widely available. Anticoagulation monitoring tests in general are feasible as they are established for VKA and heparin.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**	
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**	
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**	
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**	

	JUDGEMENT							IMPLICATIONS
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know	

Conclusions

Should measurement of the DOAC anticoagulant effect vs. no measurement of the DOAC anticoagulant effect be used during management of DOAC-related bleeding in patients receiving DOAC therapy for the treatment of VTE?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ●	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ○
RECOMMENDATION	The ASH guideline panel suggests not measuring the DOAC anticoagulant effect during management of DOAC-related bleeding in patients receiving treatment for VTE (conditional recommendation based on very low certainty in the evidence).				
JUSTIFICATION	The panel considered that there is currently no standardized DOAC tests widely available, and there is no evidence to support a beneficial effect. Therefore, the panel judged that it is better to not delay intervention for bleeding while waiting for a test result. The same considerations are applicable for emergency surgery.				
SUBGROUP CONSIDERATIONS	No subgroup considerations.				
IMPLEMENTATION CONSIDERATIONS	No implementation considerations.				

MONITORING AND EVALUATION	No monitoring and evaluation considerations.
RESEARCH PRIORITIES	The panel identified the following additional research priorities: 1) Developing validated specific DOAC effect tests 2) Testing the effect on clinical outcomes of using a validated specific DOAC test in patients with bleeding on DOAC 3) Assessing the cost-effectiveness, acceptability and feasibility of implementing a validated specific DOAC test

References for Evidence to Decision (EtD) table

1. Hogg K, Kimpton M, Carrier M, Coyle D, Forgie M, Wells P. Estimating quality of life in acute venous thrombosis. JAMA internal medicine. 2013;173(12):1067-72.
2. Hogg K, Shaw J, Coyle D, Fallah P, Carrier M, Wells P. Validity of standard gamble estimated quality of life in acute venous thrombosis. Thrombosis research. 2014;134(4):819-25.
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4. Marvig CL, Verhoef TI, de Boer A, Kamali F, Redekop K, Pirmohamed M, et al. Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants. Thrombosis research. 2015;136(1):69-75.
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6. Lenert LA, Soetikno RM. Automated computer interviews to elicit utilities: potential applications in the treatment of deep venous thrombosis. Journal of the American Medical Informatics Association : JAMIA. 1997;4(1):49-56.
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Appendix – Evidence Profile

Q20. In patients receiving DOAC therapy for the treatment of VTE should measurement of the DOAC anticoagulant effect vs. no measurement of the DOAC anticoagulant effect be used during management of DOAC-related bleeding?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**measurement of the DOAC anticoagulant effect**	**no measurement of DOAC anticoagulant effect**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality (follow up: range 30 days to 90 days)												
8 [1-8]	observational studies	very serious [a]	not serious [b]	very serious [c]	very serious [d]	none	16/79 (20.3%)	114/637 (17.9%)	RR 1.34 (0.85 to 2.12) [e]	**60 more per 1,000** (from 140 more to 30 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
PE - Moderate severity (follow up: range 30 days to 90 days; assessed with: Any thromboembolism)												
2 [1, 6]	observational studies	not serious [f]	not serious [b]	very serious [g]	not serious	none		24/497 (4.8%) [h]	not estimable		⨁◯◯◯ VERY LOW	CRITICAL
DVT in the upper leg - Moderate severity (follow up: range 30 days to 90 days; assessed with: Any thromboembolism)												
2 [1, 6]	observational studies	not serious [f]	not serious [b]	very serious [g]	not serious	none		24/497 (4.8%) [h]	not estimable		⨁◯◯◯ VERY LOW	CRITICAL
Major bleeding (follow up: 30 days; assessed with: Subsequent bleeding)												
1 [2]	observational studies	not serious [f]	not serious [b]	very serious [c,i]	not serious	none	21/55 (38.2%)		not estimable		⨁◯◯◯ VERY LOW	CRITICAL
Quality of life impairment - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Delay of intervention - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

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

Explanations

a. Very high risk of confounding as the event rate for the intervention group [1, 3, 5-7] came from different studies than the event rate for the control group [2, 4, 8]. No adjustment for important differences in study designs, populations and outcome assessment.

b. Inconsistency cannot be determined as no studies reported a direct comparison

c. Intervention groups received anticoagulation testing which was assumed to be specific to DOAC therapy, but might also have received standard anticoagulation tests such as INR/PT

d. Lower and upper bounds of the 95% CI for the anticipated absolute effect include important benefit and important harm

e. Comparison based on the pooled event rate for the intervention group and the pooled event rate of the control group. The weighted pooled event rate for each group was calculated by transforming all study event rates using the Freeman-Tukey arcsine transformation, calculating a pooled estimate of the transformed event rates, and back transforming this pooled estimate to a pooled event rate. (Freeman-Tukey 1950). The weighted pooled event rate for the intervention group was 21.2% (95% CI: 13.0-30.7%), which is different from the overall unweighted event rate of 20.3% (16/79). The weighted pooled event rate for the control group was 16.1% (95% CI: 8.3-25.8%), which is different from the overall unweighted event rate of 17.9% (114/637). Therefore, the weighted event rates of 21.2% and 16.1% respectively were used to calculate the relative effect.

f. Risk of bias cannot be assessed because the studies did not report a comparison.

g. No study reported a direct comparison. Two studies reported only a control group [1, 6]

h. Control groups only received standard anticoagulation tests such as INR/PT

i. No study reported a direct comparison. One study reported only an intervention group [2]

References – Included studies

1. Beyer-Westendorf J, Forster K, Pannach S, Ebertz F, Gelbricht V, Thieme C, et al. Rates, management, and outcome of rivaroxaban bleeding in daily care: results from the Dresden NOAC registry. Blood. 2014;124(6):955-62.
2. Beynon C, Sakowitz OW, Storzinger D, Orakcioglu B, Radbruch A, Potzy A, et al. Intracranial haemorrhage in patients treated with direct oral anticoagulants. Thromb Res. 2015;136(3):560-5.
3. Eerenberg ES, Middeldorp S, Levi M, Lensing AW, Buller HR. Clinical impact and course of major bleeding with rivaroxaban and vitamin K antagonists. J Thromb Haemost. 2015;13(9):1590-6.
4. Kumar R, Smith RE, Henry BL. A Review of and Recommendations for the Management of Patients With Life-Threatening Dabigatran-Associated Hemorrhage: A Single-Center University Hospital Experience. J Intensive Care Med. 2015;30(8):462-72.
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6. Piccini JP, Garg J, Patel MR, Lokhnygina Y, Goodman SG, Becker RC, et al. Management of major bleeding events in patients treated with rivaroxaban vs. warfarin: results from the ROCKET AF trial. Eur Heart J. 2014;35(28):1873-80.
7. Purrucker JC, Haas K, Rizos T, Khan S, Wolf M, Hennerici MG, et al. Early Clinical and Radiological Course, Management, and Outcome of Intracerebral Hemorrhage Related to New Oral Anticoagulants. JAMA Neurol. 2016;73(2):169-77.
8. Senger S, Keiner D, Hendrix P, Oertel J. New Target-Specific Oral Anticoagulants and Intracranial Bleeding: Management and Outcome in a Single-Center Case Series. World Neurosurg. 2016;88:132-9.

Question #21 – Good Practice Statement

Should renal function be monitored more frequently (every 3 months) vs. no such monitoring in patients with creatinine clearance <50 mL/min receiving DOAC therapy for treatment of VTE?

Good Practice Statement

In patients with creatinine clearance <50 mL/min receiving DOAC therapy for treatment of VTE, the ASH guideline panel believes good practice includes renal function monitoring approximately every 3 months (ungraded good practice statement).

Appendix – Support for Good Practice Statement criteria [1]

(i) Is the statement clear and actionable? Questions particular to good practice statements

Yes:

- Statement provides clear specification of procedure and timeframe

(ii) Is the message really necessary in regard to actual health care practice?

Yes:

- Most DOACs are at least partly cleared by the kidneys and renal function needs to be measured before starting treatment
- Worsening renal function (WRF) is common among patients on DOAC:
    - ROCKET AF – Rivaroxaban [2]: 26.3% among all study patients
        - WRF: >20% decrease in CrCl at any point during the study
        - Monitoring frequency: at 24 weeks and 52 weeks after randomization, at study end or early drug discontinuation, and further according to standard care
    - ARISTOTLE – Apixaban [3]: 13.6% during 12 months among all study patients
        - WRF: >20% annual decrease in eGFR
        - Monitoring frequency: every 3 months
    - Retrospective study with mix of DOACs [4]: 6.9% during 382 days among study patients with baseline eCCr ≥50 ml/min
        - WRF: eCCr <50 ml/min
        - Monitoring frequency: every few months
- Worsening renal function in patients using DOAC was associated with a higher risk of adverse events compared with patients who had stable renal function, specifically:
    - ROCKET AF – Rivaroxaban [2]: patients with WRF had a higher risk of vascular death
    - ARISTOTLE – Apixaban [3]: patients with WRF had a higher risk of stroke/SE, major bleeding and death
    - Retrospective study with mix of DOACs [4]: patients with WRF had a higher risk of major bleeding

(iii) After consideration of all relevant outcomes and potential downstream consequences, will implementing the good practice statement result in large net positive consequences?

Yes:

- Patients with diminished renal function often required a lower DOAC dose to balance optimal benefit and risk in RCTs
- Detecting worsening renal function will allow taking action according to what was part of the treatment protocols in RCTs. Based on RCT results, the panel expects that the risk of bleeding will be lowered as compared with not making treatment changes in case of undetected worsening renal function

(iv) Is collecting and summarizing the evidence a poor use of a guideline panel's limited time and energy (opportunity cost is large)?

Yes:

- The panel discussed the absence of direct evidence addressing this question, and decided that a good practice statement is most appropriate, which also saved time to address other guideline questions

(v) Is there a well-documented clear and explicit rationale connecting the indirect evidence?

Yes:

- Yes, see above

References

1. Guyatt GH, Alonso-Coello P, Schunemann HJ, Djulbegovic B, Nothacker M, Lange S, et al. Guideline panels should seldom make good practice statements: guidance from the GRADE Working Group. J Clin Epidemiol. 2016;80:3-7.
2. Fordyce CB, Hellkamp AS, Lokhnygina Y, Lindner SM, Piccini JP, Becker RC, et al. On-Treatment Outcomes in Patients With Worsening Renal Function With Rivaroxaban Compared With Warfarin: Insights From ROCKET AF. Circulation. 2016;134(1):37-47.
3. Hijazi Z, Hohnloser SH, Andersson U, Alexander JH, Hanna M, Keltai M, et al. Efficacy and Safety of Apixaban Compared With Warfarin in Patients With Atrial Fibrillation in Relation to Renal Function Over Time: Insights From the ARISTOTLE Randomized Clinical Trial. JAMA Cardiol. 2016;1(4):451-60.
4. Miyamoto K, Aiba T, Arihiro S, Watanabe M, Kokubo Y, Ishibashi K, et al. Impact of renal function deterioration on adverse events during anticoagulation therapy using non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Heart Vessels. 2016;31(8):1327-36.

Question #22

Should **initial LMWH dose selection according to actual body weight** vs. **capped LMWH doses** be used in **obese patients receiving LMWH therapy for treatment of acute VTE**?

POPULATION:	obese patients receiving LMWH therapy for treatment of acute VTE
INTERVENTION:	initial LMWH dose selection according to actual body weight
COMPARISON:	capped LMWH doses
MAIN OUTCOMES:	Mortality - Indirect comparison; PE - Moderate Severity - Indirect comparison; DVT in the Upper Leg - Moderate Severity - Indirect comparison; Major Bleeding - Indirect comparison; Quality of Life Impairment; Delay of Intervention;
SETTING:	Inpatient and outpatient
PERSPECTIVE:	Clinical recommendation - Population perspective

BACKGROUND: Low-Molecular Weight Heparins (LMWH) are important anticoagulants in venous-thromboembolism (VTE) given their reliable pharmacokinetics and efficacy in cancer associated VTE. Dosing is typically adjusted by actual body weight, but it's unclear whether that strategy is ideal for obese patients. One issue raised by pharmacokinetic studies is that these drugs do not readily diffuse into fatty tissue, suggesting this population may be overdosed. Given that obesity is such a significant and common risk factor for venous thromboembolism, identifying appropriate dosing in this patient population is important.

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Low-Molecular Weight Heparins (LMWH) are important anticoagulants in venous-thromboembolism (VTE) given their reliable pharmacokinetics and efficacy in cancer associated VTE. Dosing is typically adjusted by actual body weight, but it's unclear whether that strategy is ideal for obese patients. One issue raised by pharmacokinetic studies is that these drugs do not readily diffuse into fatty tissue, suggesting this population may be overdosed. Given that obesity is such a significant and common risk factor for venous thromboembolism, identifying appropriate dosing in this patient population is important.	
DESIRABLE	**How substantial are the desirable anticipated effects?** ● Trivial ○ Small	For research evidence on Desirable and Undesirable anticipated effects, as well as the certainty of this evidence, see the **Evidence Profile** in the **Appendix**.	The panel judged this based on a trivial

	○ Moderate ○ Large ○ Varies ○ Don't know		reduction in thromboembolism.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know		The panel could not make a judgement due to a lack of evidence. One panel member disagreed with this judgement.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies		Very low certainty in evidence for effects due to very serious risk of bias, very serious indirectness and serious imprecision.
VALUES	**Is there important uncertainty about or variability in 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	**Utility related information - the relative importance of outcomes** *Relative importance of the outcomes on a scale 0.00-1.00 with 1.00 indicating a patient comparing the outcome with being in 'Full health' and 0.00 comparing the outcome with being 'Dead'* <u>Our systematic review found that the relative importance of the outcomes is as follows:</u> - Pulmonary embolism: 0.63-0.93 (different methods) [1-3] - Deep vein thrombosis: 0.64-0.99 (different methods) [1-5]	

		- Deep vein thrombosis patients' own current health: 0.95 (Time trade off) [3] - Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) [1, 3] - Muscular bleeding: 0.76 (time trade off) [3] - Minor intracranial bleeding event: 0.75 (standard gamble) [1] - Major intracranial bleeding event: 0.15 (standard gamble) [1] - Central nervous system bleeding: 0.29-0.60 (standard gamble) [6, 7]	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know	Although effect estimates were provided, the very low quality of the evidence (primarily due to the indirect comparisons and imprecision) makes it highly uncertain what the balance of the desirable and undesirable effects is.	Very low quality evidence showed trivial desirable effect and unknown undesirable effect, with possibly important uncertainty or variability in how much people value the outcomes. Due to very serious risk of bias, indirectness and serious imprecision the panel considered the evidence to be of such low certainty that no judgement could be made for the balance of effects.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**The following economic analyses were identified:** <u>Cost of medication</u> - LMWH, per week: $199.92 - $712.00 [8] <u>Cost of clinical events</u> Cost of PE (event cost): $11,616 [9] Cost of recurrent VTE (outpatient, hospitalization, and pharmacy cost in 1-year following VTE event): $11,120 [10]	The panel judged that dosing based on actual body weight will be somewhat more expensive than using capped dosing.

		Cost of bleeding: [10] - 6 months following DVT: $11,018 for patients with major bleed - Per-event cost estimated over variable follow-up (mean follow-up = 21.3 months): $22,885 for bleed event requiring hospitalization - Per-event cost: base case treatment of bleeds = $9,935	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ● Low ○ Moderate ○ High ○ No included studies		
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	The panel could not make a judgement as no cost-effectiveness studies were identified, and it is unknown if the moderate increase in costs would be offset by fewer clinical events.
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified.	The panel judged that all patients will receive the LMWH dose recommended by institutional norms and equity will not be affected.

ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified.	The panel judged that the intervention is probably acceptable, even if it leads to extra injections and higher out-of-pocket costs.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence identified.	The panel judged that the intervention is currently being used in obese patients.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**	
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies	

	JUDGEMENT							IMPLICATIONS
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**	
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**	
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know	

Conclusions

Should initial LMWH dose selection according to actual body weight vs. capped LMWH doses be used in obese patients receiving LMWH therapy for treatment of acute VTE?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ●	Strong recommendation for the intervention ○
RECOMMENDATION	The ASH guideline panel suggests initial LMWH dose selection according to actual body weight rather than dose selection based on capped doses in obese patients receiving treatment for acute VTE (conditional recommendation based on very low certainty in the evidence).				
JUSTIFICATION	The panel suggests to use the intervention primarily due to its acceptability and feasibility, as the balance of effects was uncertain and no information is available for cost-effectiveness.				
SUBGROUP CONSIDERATIONS	No subgroup considerations.				
IMPLEMENTATION CONSIDERATIONS	No implementation considerations.				
MONITORING AND EVALUATION	No monitoring and evaluation considerations.				
RESEARCH PRIORITIES	The panel identified the following additional research priority: Comparative evidence for different LMWH initiation dosing strategies in obese VTE patients				

References for Evidence to Decision (EtD) table

1. Hogg K, Kimpton M, Carrier M, Coyle D, Forgie M, Wells P. Estimating quality of life in acute venous thrombosis. JAMA internal medicine. 2013;173(12):1067-72.
2. Hogg K, Shaw J, Coyle D, Fallah P, Carrier M, Wells P. Validity of standard gamble estimated quality of life in acute venous thrombosis. Thrombosis research. 2014;134(4):819-25.
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10. Grosse SD, Nelson RE, Nyarko KA, Richardson LC, Raskob GE. The economic burden of incident venous thromboembolism in the United States: A review of estimated attributable healthcare costs. Thromb Res. 2016;137:3-10.

Appendix – Evidence Profile

Q22. Should initial LMWH dose selection according to actual body weight vs. capped LMWH doses be used for obese patients receiving LMWH therapy for treatment of acute VTE?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	initial LMWH dose selection according to actual body weight	capped doses	Relative (95% CI)	Absolute (95% CI)		
Mortality - Indirect comparison (follow up: mean 2 weeks) [a]												
2 [1, 2]	observational studies	very serious [b]	not serious [c]	serious [d]	very serious [e]	none	0/193 (0.0%)	0/47 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	CRITICAL
PE - Moderate Severity - Indirect comparison (follow up: mean 2 weeks; assessed with: Any Venous Thromboembolism) [a]												
5 [1-5]	observational studies	very serious [f]	not serious [c]	serious [d]	very serious [g]	none	22/1739 (1.3%) [i]	1/47 (2.1%)	RR 0.84 (0.12 to 6.01) [h]	**3 fewer per 1,000** (from 19 fewer to 107 more)	⨁◯◯◯ VERY LOW	CRITICAL
DVT in the Upper Leg - Moderate Severity - Indirect comparison (follow up: mean 2 weeks; assessed with: Any Venous Thromboembolism) [a]												
5 [1-5]	observational studies	very serious [f]	not serious [c]	serious [g]	very serious [g]	none	22/1739 (1.3%) [i]	1/47 (2.1%)	RR 0.84 (0.12 to 6.01) [h]	**3 fewer per 1,000** (from 19 fewer to 107 more)	⨁◯◯◯ VERY LOW	CRITICAL
Major Bleeding - Indirect comparison (follow up: mean 2 weeks) [a]												
5 [1-5]	observational studies	very serious [f]	not serious [c]	serious [g]	very serious [g]	none	12/2373 (0.5%) [j]	0/47 (0.0%)	not estimable	**5 more per 1,000** (from -- to --) [i]	⨁◯◯◯ VERY LOW	CRITICAL
Quality of Life Impairment - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Delay of Intervention - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

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

Explanations

a. Studies reported varying follow-up lengths, but event rates were standardized to 2 weeks.

b. Very high risk of confounding as the event rate for the intervention group [1] came from a different study than the event rate for the control group [2]. No adjustment for important differences in study designs, populations and outcome assessment.

c. Inconsistency cannot be determined as no studies reported a direct comparison.

d. Indications for VKA were mainly non-VTE indications, few patients had VTE as indication.

e. Small studies with no events.

f. Very high risk of confounding as the event rate for the intervention group [1,3-5] came from a different study than the event rate for the control group [2]. No adjustment for important differences in study designs, populations and outcome assessment.

g. Lower and upper bounds of the 95% CI for the anticipated absolute effect include important benefit and important harm.

h. Comparison based on the pooled event rate for the intervention group and the event rate of the control study. The weighted pooled event rate for the intervention group was calculated by transforming all study event rates using the Freeman-Tukey arcsine transformation, calculating a pooled estimate of the transformed event rates, and back transforming this pooled estimate to a pooled event rate. (Freeman-Tukey 1950). The weighted pooled event rate for the intervention group was 1.8% (95% CI: 0.4-4.1%), which is different from the overall unweighted event rate of 1.3% (22/1739). Therefore, the weighted event rate of 1.8% was used to calculate the relative effect.

i. No Major Bleeding events in the Control group, RR and CI were not calculated.

References – Included Studies

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Question #23

Should **peri-procedureal bridging with LMWH or UHF** vs. **interruption of VKA therapy alone** be used for **patients at low to moderate risk of recurrent VTE who require interruption of VKA therapy for invasive procedures**?

POPULATION:	patients at low to moderate risk of recurrent VTE who require interruption of VKA therapy for invasive procedures
INTERVENTION:	peri-procedureal bridging with LMWH or UHF
COMPARISON:	interruption of VKA therapy alone
MAIN OUTCOMES:	PE - Moderate severity; DVT in the upper leg - Moderate severity; Major bleeding; Mortality; Quality of Life Impairment
SETTING:	Inpatient and outpatient
PERSPECTIVE:	Clinical recommendation - population perspective

BACKGROUND: Warfarin anticoagulation is indicated for the treatment of venous thromboembolism (VTE). Anticoagulation strategies around the time of surgery are unclear. While perioperative anticoagulation guidelines exist, there is little evidence to support an optimal management strategy in patients with VTE.

In low risk situations typically bridging is not warranted. Likewise, bridging is often given to those with high risk for recurrent VTE. However, there currently is little guidance for peri-procedural management of those at low-to-moderate risk for recurrent VTE.

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Warfarin anticoagulation is indicated for the treatment of venous thromboembolism (VTE). Anticoagulation strategies around the time of surgery are unclear. While perioperative anticoagulation guidelines exist, there is little evidence to support an optimal management strategy in patients with VTE. In low risk situations typically bridging is not warranted. Likewise, bridging is often given to those with high risk for recurrent VTE. However, there currently is little guidance for peri-procedural management of those at low-to-moderate risk for recurrent VTE.	
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ● Trivial ○ Small ○ Moderate	For research evidence on Desirable and Undesirable anticipated effects, as well as the certainty of this evidence, see the **Evidence Profile** in the **Appendix**.	The included patients were mainly low risk patients and the

	○ Large ○ Varies ○ Don't know		evidence was rated down for indirectness.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know		The panel made this judgement based on the increased risk for major bleeding and delay of procedure.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ● Low ○ Moderate ○ High ○ No included studies		The panel judged there to be low certainty of evidence for critical outcomes.
VALUES	**Is there important uncertainty about or variability in 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	**Utility related information - the relative importance of outcomes** *Relative importance of the outcomes on a scale 0.00-1.00 with 1.00 indicating a patient comparing the outcome with being in 'Full health' and 0.00 comparing the outcome with being 'Dead'* <u>Our systematic review found that the relative importance of the outcomes is as follows:</u> - Pulmonary embolism: 0.63-0.93 (different methods) [1-3] - Deep vein thrombosis: 0.64-0.99 (different methods) [1-5] - Deep vein thrombosis patients' own current health: 0.95 (Time trade off) [3]	

		- Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) [1, 3] - Muscular bleeding: 0.76 (time trade off) [3] - Minor intracranial bleeding event: 0.75 (standard gamble) [1] - Major intracranial bleeding event: 0.15 (standard gamble) [1] - Central nervous system bleeding: 0.29-0.60 (standard gamble) [6, 7] - Treatment with LMWH: 0.993 (time trade off) [8] - Treatment with warfarin (as a surrogate): 0.989 (time trade off) [8]	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ● Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		The incidence of recurrent VTEs was very low in this population. Absolute increase major bleeding risk is moderate and consistent across observational studies and RCTs. The panel voted for this judgement. Of 8 voting panel members, 5 voted for 'Favors the comparison' and 3 for 'Probably favors the comparison'. One panel member without COI abstained from voting.

RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**The following economic analyses were identified:** <u>Cost of procedure-related anticoagulation</u> During pacemaker and/or defibrillator surgery in 2012-2013 USD and health care system perspective - peri-procedure comparing continued warfarin or LMWH bridging: [9] *Medications:* Warfarin: $11.57 +/- $0.64 LMWH Bridging: $353.91 +/- $15.09 *Hospitalizations:* Warfarin: $41.72 +/- $37.81 LMWH Bridging: $1,114.60 +/-$164.90 *Total costs* [Coyle 2015] Warfarin therapy $218.00 vs. LMWH bridging $2,041.00 <u>Cost of clinical events</u> Cost of PE (event cost): $11,616 [10] Cost of recurrent VTE (outpatient, hospitalization, and pharmacy cost in 1-year following VTE event): $11,120 [11] Cost of bleeding: [11] - 6 months following DVT: $11,018 for patients with major bleed - Per-event cost estimated over variable follow-up (mean follow-up = 21.3 months): $22,885 for bleed event requiring hospitalization - Per-event cost: base case treatment of bleeds = $9,935	The panel judged that the intervention has large costs, driven by the cost of bleeding events.

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ● Low ○ Moderate ○ High ○ No included studies		
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	The panel could not provide a judgment due to a lack of cost-effectiveness studies.
EQUITY	**What would be the impact on health equity?** ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified.	The panel judged that health equity would probably be reduced if the intervention were recommended as patients in lower socioeconomic strata may not be able to afford LMWH injections.

ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	A survey among US ambulatory care pharmacists showed significant variation in INR bridging practices among pharmacists with different levels of experience and prescribing privileges. No significant difference in INR bridging practice was found among pharmacists practicing in different clinical settings. [12] A French chart review among 932 patients on VKA undergoing an elective or emergency procedure showed that VKA was interrupted in 74% of elective procedures and bridged with LMWH in 69% of patients who were interrupted. According to local guidelines, bridging was not used in 13% of high-risk patients who required it and was overused in 60% of low-risk patients. [13] In a Canadian retrospective study among 129 patients undergoing device surgery while on chronic oral anticoagulation showed that 76% of moderate/high risk patients received perioperative anticoagulation, but only 40% were bridged both pre- and postprocedure or maintained on uninterrupted warfarin. In the low risk group, 33% received bridging therapy. [14] A survey of 1686 US patients on anticoagulation therapy who were followed for more than one year showed that within the previous year, 50% of patients had received at least one peri-procedural request to interrupt warfarin therapy. Of all requests for therapy interruption, 48% (50% for atrial fibrillation patients) were not supported by guidelines. [15] A UK survey among cardiologists from 72 hospitals showed that there is significant variation in management of patients on anticoagulation undergoing pacemaker implantation. [16] A US retrospective study among 100 patients receiving LMWH bridging for VKA initiation showed that the mean total duration of LMWH therapy was 12.0 ± 8.2 days, of which 9.8 ± 8.0 days (median 7.5 days; interquartile range 4.3–13.0 days) occurred in the outpatient setting. 41% percent of patients received outpatient LMWH for < 7 days, 40% for 7–14 days, and 19% for > 14 days. [17]	The panel considered that patients may be biased in favor of LMWH bridging because it has become common practice and they may have received it with previous procedures.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		The panel judged that the intervention is feasible as it is currently being used in clinical practice.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know	
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	**Favors the comparison**	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**	

	JUDGEMENT							IMPLICATIONS
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know	

Should peri-procedureal bridging with LMWH or UHF vs. interruption of VKA therapy alone be used in patients at low to moderate risk of recurrent VTE who require interruption of VKA therapy for invasive procedures?

Type of recommendation

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	●	○	○	○	○

Conclusions

RECOMMENDATION	The ASH guideline panel recommends against peri-procedural bridging with LMWH or UHF during interruption of VKA therapy in patients at low to moderate risk of recurrent VTE who require invasive procedures (strong recommendation based on low certainty in the evidence). Remarks:

	- The population of interest for this question is patients undergoing any type of surgery for which interruption or bridging is considered. Many patients in the included studies were undergoing outpatient invasive procedures (e.g. colonoscopy, endoscopy, minor surgical procedures). - Bridging was defined as full dose, therapeutic LMWH or UFH. Most patients received LMWH bridging. Prophylactic perioperative dosing was not covered by this recommendation and is addressed by guidelines on perioperative prophylaxis.
JUSTIFICATION	The panel made this judgement based on low certainty evidence for trivial benefits and moderate certainty evidence for moderate harms, and large costs of the intervention.
SUBGROUP CONSIDERATIONS	No subgroup considerations.
IMPLEMENTATION CONSIDERATIONS	The bridging strategy and low-to-moderate risk group should be clearly defined.
MONITORING AND EVALUATION	No monitoring and evaluation considerations.
RESEARCH PRIORITIES	The panel identified the following additional research priority: Sufficiently powered RCTs comparing LMWH/UFH bridging vs. VKA interruption alone in VTE patients at low-to-moderate risk undergoing an invasive procedure

References for Evidence to Decision (EtD) table

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12. Maxwell WD, Shrader SP, Moore KG, Lu ZK, White SF. Survey of pharmacists' subtherapeutic INR management and anticoagulation bridging practices. J Clin Pharm Ther. 2015.
13. Steib A, Mertes PM, Marret E, Albaladejo P, Fusciardi J. Compliance with guidelines for the perioperative management of vitamin K antagonists. Thrombosis research. 2014;133(6):1056-60.
14. Perrin MJ, Vezi BZ, Ha AC, Keren A, Nery PB, Birnie DH. Anticoagulation bridging around device surgery: compliance with guidelines. Pacing Clin Electrophysiol. 2012;35(12):1480-6.
15. Skolarus LE, Morgenstern LB, Froehlich JB, Lisabeth LD, Brown DL. Guideline-discordant periprocedural interruptions in warfarin therapy. Circ Cardiovasc Qual Outcomes. 2011;4(2):206-10.
16. de Bono J, Nazir S, Ruparelia N, Bashir Y, Betts T, Rajappan K. Perioperative management of anticoagulation during device implantation-the UK perspective. Pacing Clin Electrophysiol. 2010;33(4):389-93.
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Appendix – Evidence Profile

Q23. In patients at low to moderate risk of recurrent VTE who require interruption of VKA therapy for invasive procedures should peri-procedural bridging with LMWH or UHF vs. interruption of VKA therapy alone be used?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	peri-procedureal bridging with LMWH or UHF	interruption of VKA therapy alone	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: 30 days)												
1 [1]	observational studies	not serious	not serious [a]	not serious	not serious [b]	none	0/519 (0.0%)	0/1236 (0.0%)	not estimable	**0 fewer per 1,000** (from 0 fewer to 0 fewer) [b]	⨁⨁◯◯ LOW	CRITICAL
PE - Moderate severity - not reported												
-	-	-	-	-	-	-					-	
DVT in the upper leg - Moderate severity (follow up: 30 days; assessed with: Recurrent VTE)												
1 [1]	observational studies	serious [c]	not serious [a]	serious [d]	serious [e]	none	0/519 (0.0%)	3/1236 (0.2%)	OR 0.34 (0.02 to 6.58)	**2 fewer per 1,000** (from 2 fewer to 13 more)	⨁◯◯◯ VERY LOW	CRITICAL
Major Bleeding (follow up: 30 days; assessed with: Clinically relevant bleeding)												
1 [1]	observational studies	serious [c]	not serious [a]	not serious	serious [f]	none [g]	13/519 (2.5%)	1/1236 (0.1%)	RR 31.73 (4.14 to 243.19)	**25 more per 1,000** (from 3 more to 196 more)	⨁◯◯◯ VERY LOW	CRITICAL
QoL Impairment (assessed with: Patient satisfaction: 7-point Likert scale; 1-"very dissatisfied" to 7-"very satisfied"; Scale from: 1 to 7)												
1 [2]	randomised trials	serious [h]	not serious [a]	serious [i,j]	not serious	none	5.9	6.4	-	MD **0.5 lower** (0.25 lower to 0.75 lower)	⨁⨁◯◯ LOW	CRITICAL
Delay of Intervention (assessed with: prolonged hospitalization; hematoma requiring interruption of anticoagulation or evacuation)[k]												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	peri-procedureal bridging with LMWH or UHF	interruption of VKA therapy alone	Relative (95% CI)	Absolute (95% CI)		
1 [2]	randomised trials	serious [h]	not serious [a]	serious [j,l]	not serious	none	54/338 (16.0%)	12/343 (3.5%)	RR 4.57 (2.49 to 8.38)	**125 more per 1,000** (from 52 more to 258 more)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **OR:** Odds ratio; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Inconsistency cannot be determined as only one study reported the outcome

b. No events in both groups.

c. Retrospective analysis using administrative data; adjustment for confounders was not possible due to very low event rates

d. Outcome included any VTE, not only DVT

e. Lower and upper bounds of the 95% CI for the anticipated absolute effect include important benefit and important harm

f. Lower and upper bounds of the 95% CI for the anticipated absolute effect include small harm and very large harm

g. Although the effect is very large, the number of events is small and only one study is available. Thus, the evidence is not upgraded for a large effect.

h. Envelopes were used to conceal allocation as part of the randomization process.

i. Patient satisfaction was used as surrogate for quality of life impairment

j. Patients underwent pacemaker/defibrillator surgery, only 5% had VTE as VKA indication

k. pacemaker/defibrillator surgery (control continued warfarin unless forced to interrupt) [Birnie 2013 - table 3]

l. The control group did not interrupt VKA, but continued VKA during the procedure.

References – Included studies

1. Clark NP, Witt DM, Davies LE, Saito EM, McCool KH, Douketis JD, et al. Bleeding, Recurrent Venous Thromboembolism, and Mortality Risks During Warfarin Interruption for Invasive Procedures. JAMA Intern Med. 2015;175(7):1163-8.
2. Birnie DH, Healey JS, Wells GA, Verma A, Tang AS, Krahn AD, et al. Pacemaker or defibrillator surgery without interruption of anticoagulation. N Engl J Med. 2013;368(22):2084-93.

Question #24

Should **confirmation of absence of DOAC anticoagulant effect** be used vs. **interrupting DOAC therapy alone** in **patients interrupting DOAC therapy for invasive procedures**?

POPULATION:	patients interrupting DOAC therapy for invasive procedures	**BACKGROUND:**	While direct oral anticoagulants (DOACs) have been considered to not require routine laboratory monitoring, certain situations may warrant such monitoring. The perioperative setting represents one such situation. DOACs are usually discontinued in this setting, but there remains debate regarding whether routinely confirming the absence of anticoagulant effect provides more benefit over a 'pharmacokinetic approach' involving simple discontinuation and re-initiation based on the DOAC's pharmacokinetic profile.
INTERVENTION:	confirmation of absence of DOAC anticoagulant effect		
COMPARISON:	Interrupting DOAC therapy alone		
MAIN OUTCOMES:	Mortality; PE - Moderate severity; DVT in the upper leg - Moderate severity; Major bleeding; Quality of life impairment; Delay of intervention;		
SETTING:	Inpatient and outpatient		
PERSPECTIVE:	Clinical recommendation - Population perspective		

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	While direct oral anticoagulants (DOACs) have been considered to not require routine laboratory monitoring, certain situations may warrant such monitoring. The perioperative setting represents one such situation. DOACs are usually discontinued in this setting, but there remains debate regarding whether routinely confirming the absence of anticoagulant effect provides more benefit over a 'pharmacokinetic approach' involving simple discontinuation and re-initiation based on the DOAC's pharmacokinetic profile.	
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ● Trivial ○ Small ○ Moderate	For research evidence on Desirable and Undesirable anticipated effects, as well as the certainty of this evidence, see the **Evidence Profile** in the **Appendix**.	

	○ Large ○ Varies ○ Don't know		
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies		Very low certainty in evidence for effects due to very serious risk of bias, indirectness and serious imprecision.
VALUES	**Is there important uncertainty about or variability in 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	**Utility related information - the relative importance of outcomes** *Relative importance of the outcomes on a scale 0.00-1.00 with 1.00 indicating a patient comparing the outcome with being in 'Full health' and 0.00 comparing the outcome with being 'Dead'* <u>Our systematic review found that the relative importance of the outcomes is as follows:</u> - Pulmonary embolism: 0.63-0.93 (different methods) [1-3] - Deep vein thrombosis: 0.64-0.99 (different methods) [1-5] - Deep vein thrombosis patients' own current health: 0.95 (Time trade off) [2]	

		- Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) [1, 2] - Muscular bleeding: 0.76 (time trade off) [2] - Minor intracranial bleeding event: 0.75 (standard gamble) [1] - Major intracranial bleeding event: 0.15 (standard gamble) [1] - Central nervous system bleeding: 0.29-0.60 (standard gamble) [6, 7]	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know	Although effect estimates were provided, the very low quality of the evidence (primarily due to the indirectness regarding population, intervention and comparisons) makes it highly uncertain what the balance of the desirable and undesirable effects is.	Very low quality evidence showed trivial desirable and undesirable effects, with possibly important uncertainty or variability in how much people value the outcomes. Due to very serious risk of bias, indirectness and serious imprecision the panel considered the evidence to be of such low certainty that no judgement could be made for the balance of effects.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know	**The following economic analyses were identified:** <u>Cost of laboratory tests</u> Laboratory test costs (USD) (University of Nevada Las Vegas Quest Diagnostics Vendor Fee Schedule, 2016): - CBC with differential: $12.67 - PT (Prothrombin Time) + INR: $3.22 - PTT (Partial Thromboplastin Time): $6.30 - TT (Thrombin Time): $26.25 - Factor X Activity: $53.20 <u>Cost of clinical events</u>	The panel could not make a judgement as the use of monitoring assays may increase costs, also by postponing procedures if elevated, but could lead to cost savings if bleedings are prevented.

		Cost of PE (event cost): $11,616 [8] Cost of recurrent VTE (outpatient, hospitalization, and pharmacy cost in 1-year following VTE event): $11,120 [9] Cost of bleeding: [9] - 6 months following DVT: $11,018 for patients with major bleed - Per-event cost estimated over variable follow-up (mean follow-up = 21.3 months): $22,885 for bleed event requiring hospitalization - Per-event cost: base case treatment of bleeds = $9,935	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ● Low ○ Moderate ○ High ○ No included studies		
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	No research evidence identified.	The panel could not make a judgement as no cost-effectiveness studies were identified, and it is unknown if there is a difference in cost and whether a higher cost would be offset by fewer clinical events.

EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ● Don't know	No research evidence identified.	The panel judged that if a specific DOAC test were available in hospitals, all patients undergoing a procedure would receive the test. It is also possible that a given test might not be available in all hospitals.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified.	Anticoagulation monitoring tests are acceptable as they are currently being used, but it is uncertain if postponing a procedure would be acceptable in case of an elevated result.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence identified.	The panel judged that the intervention is probably feasible if a validated test is widely available. Anticoagulation monitoring tests in general are feasible as they are established for VKA and heparin.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know	

	JUDGEMENT							IMPLICATIONS
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know	
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**	
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**	
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**	
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know	

Conclusions

Should confirmation of absence of DOAC anticoagulant effect be used vs. interrupting DOAC therapy alone in patients interrupting DOAC therapy for invasive procedures?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ●	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ○
RECOMMENDATION	The ASH guideline panel suggests not confirming the absence of DOAC anticoagulant effect prior to procedures in patients interrupting DOAC therapy for invasive procedures (conditional recommendation based on very low certainty in the evidence).				
JUSTIFICATION	The panel made this judgement due to uncertainty about how good current tests are at confirming the absence or presence of DOAC, and the lack of standardization of tests. Remark: certain subgroups might benefit from DOAC testing, see 'Subgroup considerations'.				
SUBGROUP CONSIDERATIONS	The panel acknowledges that testing for the absence of DOAC anticoagulant effect might be considered prior to a very high bleeding risk procedure, or in patients at high risk of bleeding or with renal function compromise.				
IMPLEMENTATION CONSIDERATIONS	No implementation considerations.				
MONITORING AND EVALUATION	No monitoring and evaluation considerations.				
RESEARCH PRIORITIES	The panel identified the following additional research priorities: 1) Developing validated specific DOAC effect tests 2) Testing the effect on clinical outcomes of using a validated specific DOAC test in patients on DOAC who need to undergo a procedure 3) Assessing the cost-effectiveness, acceptability and feasibility of implementing a validated specific DOAC test				

References for Evidence to Decision (EtD) table

1. Hogg K, Kimpton M, Carrier M, Coyle D, Forgie M, Wells P. Estimating quality of life in acute venous thrombosis. JAMA internal medicine. 2013;173(12):1067-72.
2. Locadia M, Bossuyt PM, Stalmeier PF, Sprangers MA, van Dongen CJ, Middeldorp S, et al. Treatment of venous thromboembolism with vitamin K antagonists: patients' health state valuations and treatment preferences. Thrombosis and haemostasis. 2004;92(6):1336-41.
3. Hogg K, Shaw J, Coyle D, Fallah P, Carrier M, Wells P. Validity of standard gamble estimated quality of life in acute venous thrombosis. Thrombosis research. 2014;134(4):819-25.
4. Marvig CL, Verhoef TI, de Boer A, Kamali F, Redekop K, Pirmohamed M, et al. Quality of life in patients with venous thromboembolism and atrial fibrillation treated with coumarin anticoagulants. Thrombosis research. 2015;136(1):69-75.
5. Utne KK, Tavoly M, Wik HS, Jelsness-Jorgensen LP, Holst R, Sandset PM, et al. Health-related quality of life after deep vein thrombosis. SpringerPlus. 2016;5(1):1278.
6. Lenert LA, Soetikno RM. Automated computer interviews to elicit utilities: potential applications in the treatment of deep venous thrombosis. Journal of the American Medical Informatics Association : JAMIA. 1997;4(1):49-56.
7. O'Meara JJ, 3rd, McNutt RA, Evans AT, Moore SW, Downs SM. A decision analysis of streptokinase plus heparin as compared with heparin alone for deep-vein thrombosis. The New England journal of medicine. 1994;330(26):1864-9.
8. Saunders RJ, Ozols AA. Cost burden of venous thromboembolism and its prophylaxis in the United States. 2016.
9. Grosse SD, Nelson RE, Nyarko KA, Richardson LC, Raskob GE. The economic burden of incident venous thromboembolism in the United States: A review of estimated attributable healthcare costs. Thromb Res. 2016;137:3-10.

Appendix – Evidence Profile

Q24. In patients interrupting DOAC therapy for invasive procedures should confirmation of absence of DOAC anticoagulant effect be used vs. interrupting DOAC therapy alone?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	omitting DOAC doses prior to a procedure plus confirmation of absence of DOAC anticoagulant effect	omitting DOAC doses prior to procedure alone	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: mean 30 days)												
3 [1-3]	observational studies	very serious [a]	not serious [b]	serious [c]	very serious [d]	none	4/722 (0.6%)	6/676 (0.9%)	RR 0.62 (0.18 to 2.20) [e]	**3 fewer per 1,000** (from 7 fewer to 11 more)	⨁◯◯◯ VERY LOW	CRITICAL
PE - Moderate severity (follow up: range 7 days to 5 months; assessed with: Any thromboembolism) [i]												
5 [1-5]	observational studies	very serious [g]	not serious [b]	serious [c]	serious [d]	none	2/787 (0.4%)	8/867 (0.7%)	RR 0.55 (0.14 to 2.20) [h]	**3 fewer per 1,000** (from 6 fewer to 8 more)	⨁◯◯◯ VERY LOW	CRITICAL
DVT in the upper leg - Moderate severity (follow up: range 7 days to 5 months; assessed with: Any thromboembolism) [i]												
5 [1-5]	observational studies	very serious [g]	not serious [b]	serious [c]	serious [d]	none	2/787 (0.4%)	8/867 (0.7%)	RR 0.55 (0.14 to 2.20) [h]	**3 fewer per 1,000** (from 6 fewer to 8 more)	⨁◯◯◯ VERY LOW	CRITICAL
Major bleeding (follow up: range 7 days to 5 months) [i]												
5 [1-5]	observational studies	very serious [g]	not serious [b]	not serious	very serious [d]	none	14/787 (1.9%)	14/867 (1.7%)	RR 1.10 (0.54 to 2.24) [i]	**2 more per 1,000** (from 8 fewer to 21 more)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life impairment - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Delay of intervention - not reported												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	omitting DOAC doses prior to a procedure plus confirmation of absence of DOAC anticoagulant effect	omitting DOAC doses prior to procedure alone	Relative (95% CI)	Absolute (95% CI)		
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

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

Explanations

a. Very high risk of confounding as the event rate for the intervention group [2,3] came from different studies than the event rate for the control group [1]. No adjustment for important differences in study designs, populations and outcome assessment.

b. Inconsistency cannot be determined as no studies reported a direct comparison.

c. Indication for VKA was mainly atrial fibrillation, few patients had VTE as indication.

d. Lower and upper bounds of the 95% CI for the anticipated absolute effect include important benefit and important harm.

e. Comparison based on the pooled event rate for the intervention group and the event rate of the control study. The weighted pooled event rate for the intervention group was calculated by transforming all study event rates using the Freeman-Tukey arcsine transformation, calculating a pooled estimate of the transformed event rates, and back transforming this pooled estimate to a pooled event rate. (Freeman-Tukey 1950). The weighted pooled event rate for the intervention group was 0.5% (95% CI: 0.1-1.5%), which is similar to the overall unweighted event rate of 0.6% (4/722).Therefore, the unweighted event rate of 0.6% was used to calculate the relative effect.

f. Godier 2015 reported events during hospitalization for an invasive procedure. The assumption was made that this was on average a follow-up of 7 days.

g. Very high risk of confounding as the event rate for the intervention group [2-4] came from different studies than the event rate for the control group [1,5]. No adjustment for important differences in study designs, populations and outcome assessment.

h. Comparison based on the pooled event rate for the intervention group and the pooled event rate of the control group. The weighted pooled event rates for each group was calculated by transforming all study event rates using the Freeman-Tukey arcsine transformation, calculating a pooled estimate of the transformed event rates, and back transforming this pooled estimate to a pooled event rate. (Freeman-Tukey 1950). The weighted pooled event rate for the intervention group was 0.4% (95% CI: 0.1-0.9%), which is different from the overall unweighted event rate of 0.3% (2/787). The weighted pooled event rate for the control group was 0.6% (95% CI: 0.0-2.4%), which is different from the overall unweighted event rate of 0.9% (8/867). Therefore, the weighted event rates of 0.4% and 0.6% respectively were used to calculate the relative effect.

i. Comparison based on the pooled event rate for the intervention group and the pooled event rate of the control group. The weighted pooled event rates for each group was calculated by transforming all study event rates using the Freeman-Tukey arcsine transformation, calculating a pooled estimate of the transformed event rates, and back transforming this pooled estimate to a pooled event rate. (Freeman-Tukey 1950). The weighted pooled event rate for the intervention group was 1.9% (95% CI: 0.7-3.9%), which is different from the overall unweighted event rate of 1.8% (14/787). The weighted pooled event rate for the control group was 1.7% (95% CI: 1.0-2.7%), which is different from the overall unweighted event rate of 1.6% (14/867). Therefore, the weighted event rates of 1.9% and 1.7% respectively were used to calculate the relative effect.

References – Included Studies

1. Beyer-Westendorf J, Forster K, Pannach S, Ebertz F, Gelbricht V, Thieme C, et al. Rates, management, and outcome of rivaroxaban bleeding in daily care: results from the Dresden NOAC registry. Blood. 2014;124(6):955-62.
2. Douketis JD, Wang G, Chan N, Eikelboom JW, Syed S, Barty R, et al. Effect of standardized perioperative dabigatran interruption on the residual anticoagulation effect at the time of surgery or procedure. J Thromb Haemost. 2016;14(1):89-97.
3. Schulman S, Carrier M, Lee AY, Shivakumar S, Blostein M, Spencer FA, et al. Perioperative Management of Dabigatran: A Prospective Cohort Study. Circulation. 2015;132(3):167-73.
4. Godier A, Martin AC, Leblanc I, Mazoyer E, Horellou MH, Ibrahim F, et al. Peri-procedural management of dabigatran and rivaroxaban: Duration of anticoagulant discontinuation and drug concentrations. Thromb Res. 2015;136(4):763-8.
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Question #25

Should **LMWH or UFH bridge therapy** vs. **overlapping DOAC therapy** be used in **patients transitioning from DOAC to VKA until the INR is within the therapeutic range**?

POPULATION:	patients transitioning from DOAC to VKA until the INR is within the therapeutic range
INTERVENTION:	LMWH or UFH bridge therapy
COMPARISON:	overlapping DOAC therapy
MAIN OUTCOMES:	PE - Moderate severity; DVT in the upper leg - Moderate severity; Major bleeding; Mortality; Quality of Life Impairment
SETTING:	Inpatient and outpatient
PERSPECTIVE:	Clinical recommendation - population perspective

BACKGROUND: There is end-of-study data from DOAC clinical trials where participants were transitioned to warfarin; however, there is sparse data regarding bridging using LMWH or overlapping DOAC and VKA during the transition. In the approved prescribing information, the FDA added the following black box warning: Premature discontinuation of DOAC (rivaroxaban, dabigatran, apixaban, edoxaban) increases the risk of thrombotic events. To reduce this risk, consider coverage with another anticoagulant if DOAC discontinued for a reason other than pathological bleeding or completion of a course of therapy. Canadian packaging has no such warning. With comparatively little information regarding transitions between DOACs and other anticoagulants, there is little data available to inform those wishing/needed to switch from a DOAC to VKA.

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	There is end-of-study data from DOAC clinical trials where participants were transitioned to warfarin; however, there is sparse data regarding bridging using LMWH or overlapping DOAC and VKA during the transition. In the approved prescribing information, the FDA added the following black box warning: Premature discontinuation of DOAC (rivaroxaban, dabigatran, apixaban, edoxaban) increases the risk of thrombotic events. To reduce this risk, consider coverage with another anticoagulant if DOAC discontinued for a reason other than pathological bleeding or completion of a course of therapy. Canadian packaging has no such warning. With comparatively little information regarding transitions between DOACs and other anticoagulants, there is little data available to inform those wishing/needed to switch from a DOAC to VKA.	

DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know		The panel could not make a judgement considering the very low certainty evidence, primarily due to very serious indirectness and serious risk of bias and imprecision.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know		The panel could not make a judgement considering the very low certainty evidence, primarily due to very serious indirectness and serious risk of bias and imprecision.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies		The evidence was of very low certainty, primarily due to very serious indirectness related to the absence of evidence for VTE patients. In addition, the evidence had serious risk of bias and imprecision.
VALUES	**Is there important uncertainty about or variability in 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	**Utility related information - the relative importance of outcomes** *Relative importance of the outcomes on a scale 0.00-1.00 with 1.00 indicating a patient comparing the outcome with being in 'Full health' and 0.00 comparing the outcome with being 'Dead'* <u>Our systematic review found that the relative importance of the outcomes is as follows:</u> - Pulmonary embolism: 0.63-0.93 (different methods) [1-3]	

		- Deep vein thrombosis: 0.64-0.99 (different methods) [1-5] - Deep vein thrombosis patients' own current health: 0.95 (Time trade off) [3] - Gastrointestinal tract bleeding event: 0.65 (standard gamble and time trade off) [1, 3] - Muscular bleeding: 0.76 (time trade off) [3] - Minor intracranial bleeding event: 0.75 (standard gamble) [1] - Major intracranial bleeding event: 0.15 (standard gamble) [1] - Central nervous system bleeding: 0.29-0.60 (standard gamble) [6, 7] - Treatment with LMWH: 0.993 (time trade off) [8] - Treatment with warfarin (as a surrogate): 0.989 (time trade off) [8]	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know		The panel could not make a judgement considering the very low certainty evidence, primarily due to very serious indirectness and serious risk of bias and imprecision.
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**The following economic analyses were identified:** <u>Cost of procedure-related anticoagulation</u> In 2013 pricing through Medicare: Warfarin: Cost per week: $4.43 USD Heparin: Cost per week: $24.99 USD LMWH (dalteparin, enoxaparin): Cost per week: $152.40-$154.59 USD	The panel judged that LMWH/UFH bridge therapy will be more expensive than overlapping DOAC therapy.

		DOAC: (apixaban, rivaroxaban, edoxaban) Cost per week: $66.76-133.53 USD <u>Cost of clinical events</u> Cost of PE (event cost): $11,616 [9] Cost of recurrent VTE (outpatient, hospitalization, and pharmacy cost in 1-year following VTE event): $11,120 [10] Cost of bleeding: [10] - 6 months following DVT: $11,018 for patients with major bleed - Per-event cost estimated over variable follow-up (mean follow-up = 21.3 months): $22,885 for bleed event requiring hospitalization - Per-event cost: base case treatment of bleeds = $9,935	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ● Low ○ Moderate ○ High ○ No included studies		Costs of LMWH, UFH and DOACs are generally known.
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies	No research evidence identified.	The panel could not provide a judgment due to a lack of cost-effectiveness studies.

	● No included studies		
EQUITY	**What would be the impact on health equity?** ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence identified.	The panel judged that health equity would probably be reduced if the intervention were recommended as patient in lower socioeconomic strata may be unable to afford LMWH therapy.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence identified.	The panel judged that the intervention will probably be acceptable as patients were already taking DOAC and patients typically prefer not to take injections.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence identified.	The panel judged that the intervention is feasible as LMWH bridge therapy is commonly being used, and careful INR monitoring when transitioning to VKA is always required, regardless of bridging strategy.

Summary of judgements

	JUDGEMENT							IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**	
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	**Don't know**	
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies	
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability				
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**	
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	**Low**	Moderate	High			No included studies	
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**	

	JUDGEMENT							IMPLICATIONS
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know	
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know	
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know	

Should LMWH or UFH bridge therapy vs. overlapping DOAC therapy be used in patients transitioning from DOAC to VKA until the INR is within the therapeutic range?

Type of recommendation

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	●	○	○	○

Conclusions

RECOMMENDATION	The ASH guideline panel suggests not using LMWH or UFH bridge therapy in favor of overlapping DOAC therapy in patients on DOAC for VTE treatment and transitioning from DOAC to VKA until the INR is within the therapeutic range (conditional recommendation based on very low certainty in the evidence). Remarks: - Anonymous voting was required: of 9 voting panel members, 6 voted in favor of a conditional recommendation against the intervention (LMWH bridge therapy), and 3 voted in favor of a conditional recommendation for either the intervention or the comparison

	- Risks associated with transitioning to VKA requires careful INR monitoring - The degree of averseness to (self) injection will influence patients' choice for or against overlap with LMWH/UFH
JUSTIFICATION	The panel made this judgement based on the following considerations: - The difference in bleeding risk is likely to be small, although the panel was uncertain due to the very low certainty evidence - LWMH (and UFH) injections are a burden to patients, and they are more expensive than DOAC therapy
SUBGROUP CONSIDERATIONS	The choice to use LMWH/UFH overlap therapy should be based on patient preference (whether patients can tolerate injections and injections are affordable).
IMPLEMENTATION CONSIDERATIONS	No implementation considerations.
MONITORING AND EVALUATION	No monitoring and evaluation considerations.
RESEARCH PRIORITIES	The panel identified the following additional research priority: Sufficiently powered RCTs comparing DOAC overlap with LMWH/UFH overlap in VTE patients switching from DOAC to VKA

References for Evidence to Decision (EtD) table

1. Hogg K, Kimpton M, Carrier M, Coyle D, Forgie M, Wells P. Estimating quality of life in acute venous thrombosis. JAMA internal medicine. 2013;173(12):1067-72.
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10. Grosse SD, Nelson RE, Nyarko KA, Richardson LC, Raskob GE. The economic burden of incident venous thromboembolism in the United States: A review of estimated attributable healthcare costs. Thromb Res. 2016;137:3-10.

Appendix – Evidence Profile

Q25. Should LMWH/UFH bridge therapy vs. overlapping DOAC therapy be used for patients transitioning from DOAC to VKA until the INR is within the therapeutic range?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LMWH/UFH bridge therapy	overlapping DOAC therapy	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: 30 days)												
3 [1-3]	observational studies	not serious [a]	not serious	very serious [b,c,d]	not serious	none		49/17540 (0.3%)	not estimable		⨁◯◯◯ VERY LOW	CRITICAL
PE - moderate severity (follow up: 30 days; assessed with: Any thromboembolism)												
1 [2]	observational studies	very serious [e]	not serious [f]	very serious [b,d,g]	serious [h]	none	2/83 (2.4%)	18/4149 (0.4%)	RR 5.58 (1.32 to 23.65)	**20 more per 1,000** (from 1 more to 98 more)	⨁◯◯◯ VERY LOW	CRITICAL
DVT in upper leg - moderate severity (follow up: 30 days; assessed with: Any thromboembolism)												
1 [2]	observational studies	very serious [e]	not serious [f]	very serious [b,d,g]	serious [h]	none	2/83 (2.4%)	18/4149 (0.4%)	RR 5.58 (1.32 to 23.65)	**20 more per 1,000** (from 1 more to 98 more)	⨁◯◯◯ VERY LOW	CRITICAL
Major Bleeding (follow up: 30 days; assessed with: Hemorrhagic stroke)												
1 [2]	observational studies	very serious [e]	not serious [f]	very serious [b,d,i]	very serious [j]	none	0/83 (0.0%)	4/4508 (0.1%)	not estimable [k]		⨁◯◯◯ VERY LOW	CRITICAL
QoL Impairment - not reported												
-	-	-	-	-	-	-					-	CRITICAL

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

Explanations

a. No comparison group, risk of bias cannot be assessed

b. The study only included patients with atrial fibrillation, not VTE

c. No control group event rate was available

d. In Mahaffey 2013 patients stopped study drug at end-of-study visit, there was no overlap with VKA

e. Intervention and control groups had important differences, the bridging strategy was intended to be used by clinicians when they perceived the patient was at high risk for VTE. Comparison was not adjusted for confounding

f. Inconsistency cannot be determined as only one study reported the outcome

g. The thromboembolic outcome was stroke only

h. Lower and upper bounds of the 95% CI for the anticipated absolute effect include trivial benefit and very important benefit

i. Outcome includes only hemorrhagic stroke, not any major bleeding

j. Lower and upper bounds of the 95% CI for the anticipated absolute effect include important benefit and important benefit

k. Due to the very low event rates in both groups, the relative risk and 95% CI were not reliable and are therefore not reported.

References – Included studies

1. Granger CB, Lopes RD, Hanna M, Ansell J, Hylek EM, Alexander JH, et al. Clinical events after transitioning from apixaban versus warfarin to warfarin at the end of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial. Am Heart J. 2015;169(1):25-30.
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