DURATION OF ANTICOAGULATION FOR THE TREATMENT OF VTE

UK THROMBOSIS DAY, TEMPLEPATRICK, 15.5.19

Dr. Chris McCauley, Belfast City Hospital

OUTLINE

1.EVIDENCE
2.PRACTICAL APPROACHES
3.GUIDELINES
4. QUIZ if time
(not covering cancer associated thrombosis)

1. Evidence for shorter duration of initial treatment

4-6 weeks *vs*. 3-6 months.—

Four studies involving 1988 patients with a first unprovoked DVT (mainly proximal) or PE compared 4-6 weeks anticoagulation with VKA with three or six months. Follow-up was 1-2 years.

	4-6weeks anticoagulation	3-6 months anticoagulation
VTE recurrence	12.6%	6.7%
Major Bleeding	0.61%	1%

2. Evidence for Longer duration of initial Treatment

Three months *vs*. 6-12 months.—

Four studies involving 1,736 patients with first unprovoked DVT (mainly proximal) or PE compared three months of anticoagulation with VKA with six or 12 months. Follow-up was one to three

years.

	3 months anticoagulation	6-12 months anticoagulation
VTE recurrence	9.7%	9.6%
Major Bleeding	0.93%	2.4%

3. Evidence for indefinite Anticoagulation

3-6 months *vs.* indefinite anticoagulation

Four studies involving 676 patients, themajority with second unprovoked DVT (mainly

proximal) or PE compared 3-6 months of anticoagulation with VKA (INR 2-3) with indefinite duration of anticoagulation. Follow-up was 1.4 to four years.

	3-6 months anticoagulation	INDEFINITE anticoagulation
VTE recurrence	18.8%	2.7%
Major Bleeding	1.5%	4.6%

4. Evidence for Recurrence Risk

Rate of venous thromboembolism (VTE) recurrence

VTE type	First year	5 years
First episode of unprovoked VTE	10 percent	30 percent
Second episode of unprovoked VTE	15 percent	45 percent
First VTE provoked by surgery	1 percent	3 percent
First VTE provoked by non-surgical factor	5 percent	15 percent

5. Evidence for Bleeding Risk

Risk factors for bleeding with anticoagulant therapy and estimated risk of major bleeding in low, moderate, and high risk categories

Risk factors*
Age >65 years
Age >75 years
Previous bleeding
Cancer
Metastatic cancer
Renal failure
Liver failure
Thrombocytopenia
Previous stroke
Diabetes
Anemia
Antiplatelet therapy
Poor anticoagulant control
Comorbidity and reduced functional capacity
Recent surgery¶
Frequent falls
Alcohol abuse

Estimated absolute risk of major bleeding (%)			
Categorization of risk of bleeding$^{\Delta}$	**Low risk$^{\diamond}$ (0 risk factors)**	**Moderate risk$^{\diamond}$ (1 risk factor)**	**High risk$^{\diamond}$ (≥2 risk factors)**
Anticoagulation 0 to 3 months§			
Baseline risk (%)	0.6	1.2	4.8
Increased risk (%)	1	2	8
Total risk (%)	1.6§	3.2	12.8$^{¥}$
Anticoagulation after first 3 months‡			
Baseline risk (%/years)	0.3†	0.6	≥2.5
Increased risk (%/years)	0.5	1	≥4
Total risk (%/years)	0.8**	1.6**	≥6.5

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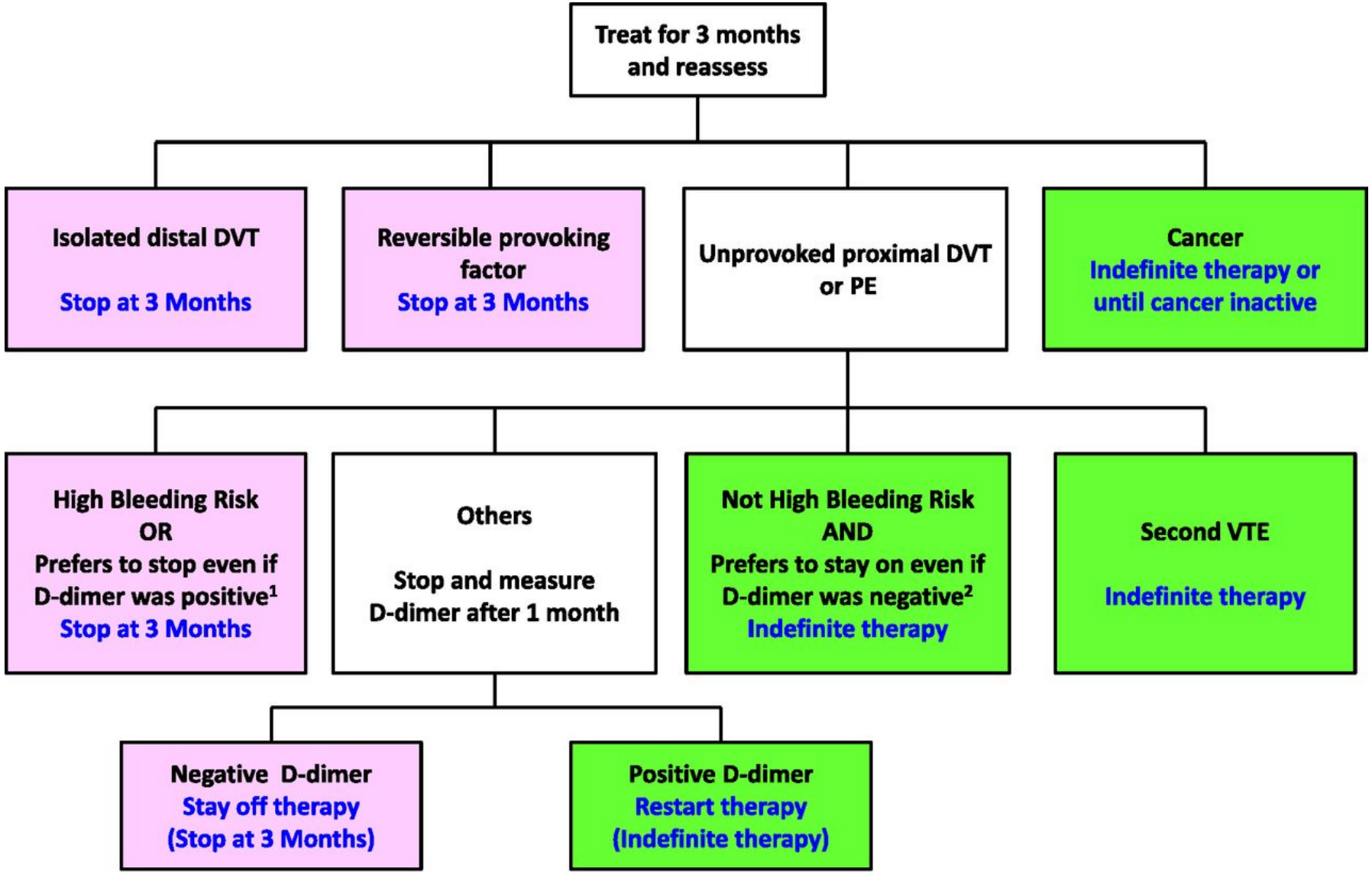
References for Evidence

1. Kearon C, Gent M, Hirsh J, Weitz J, Kovacs MJ, AndersonDR, *et al.* A comparison of three months of anticoagulation with extended anticoagulation for a first episodeof idiopathic venous thromboembolism. N Engl J Med.1999;340:901-7.
2. Schulman S, Granqvist S, Holmstrom M, Carlsson A,Lindmarker P, Nicol P, *et al.* The duration of oral anticoagulanttherapy after a second episode of venous thromboembolism. The Duration of AnticoagulationTrial Study Group. N Engl J Med. 1997;336:393-8.
3. 107. Levine MN, Hirsh J, Gent M, Turpie AG, Weitz J, GinsbergJ, *et al.* Optimal duration of oral anticoagulanttherapy: a randomized trial comparing four weeks withthree months of warfarin in patients with proximaldeep vein thrombosis. Thromb Haemost. 1995;74:606-11.
4. Optimum duration of anticoagulation for deep-veinthrombosis and pulmonary embolism. ResearchCommittee of the British Thoracic Society. Lancet.1992;340:873-6
5. Pinede L, Ninet J, Duhaut P, Chabaud S, Demolombe-Rague S, Durieu I, *et al.* Comparison of 3 and 6 monthsoforalanticoagulant therapy after a first episode ofproximal deep vein thrombosis or pulmonary embolismandcomparison of 6 and 12 weeks of therapy after isolated calf deep vein thrombosis. Circulation. 2001;103:2453-60.
6. Schulman S, Rhedin AS, Lindmarker P, Carlsson A,Larfars G, Nicol P, *et al.* A comparison of six weeks with six months of oral anticoagulant therapy after afirst episode of venous thromboembolism. Durationof Anticoagulation TrialStudy Group. N Engl J Med.1995;332:1661-5.
7. Agnelli G, Prandoni P, Becattini C, Silingardi M, TalianiMR, Miccio M, *et al.* Extended oral anticoagulanttherapy after a firstepisode of pulmonary embolism.Ann Intern Med. 2003;139:19-25.
8. Kearon C, Ginsberg JS, Anderson DR, Kovacs MJ,Wells P, Julian JA, *et al.* Comparison of 1 month with 3months of anticoagulation for a first episode of venousthromboembolism associated with a transient risk factor.J Thromb Haemost. 2004;2:743-9
9. Agnelli G, Prandoni P, Santamaria MG, Bagatella P, IorioA, Bazzan M, *et al.* Three months versus one year oforal anticoagulant therapy for idiopathic deep venousthrombosis. Warfarin Optimal Duration Italian TrialInvestigators. N Engl J Med. 2001;345:165-9.
10. Campbell IA, Bentley DP, Prescott RJ, Routledge PA,Shetty HG, Williamson IJ. Anticoagulation for threeversus six months in patients with deep vein thrombosisor pulmonary embolism, or both: randomised trial.Br Med J. 2007;334:674-80.
11. Palareti G, Cosmi B, Legnani C, Tosetto A, Brusi C, IorioA, *et al.* D-dimer testing to determine the duration ofanticoagulation therapy. N Engl J Med. 2006;355:1780-9.
12. Farraj RS. Anticoagulation period in idiopathic venousthromboembolism. How long is enough? Saudi Med J. 2004;25:848-51.
13. Hull RD, Raskob GE, Rosenbloom D, et al. Heparin for 5 days as compared with 10 days in the initial treatment of proximal venous thrombosis. N Engl J Med 1990; 322:1260.
14.Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141:e419S.

Practical Approaches

Patients with VTE who should be treated for 3 months and who should be treated indefinitely.



Clive Kearon, and Elie A. Akl Blood 2014;123:1794-1801

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Practical Approaches

1. Provoking Factors

VTE PROVOKED BY A TRANSIENT RISK FACTOR*

Major transient risk factor during the 3 months before diagnosis of VTE

- Surgery with general anesthesia for greater than 30 min.
- Confined to bed in hospital (only 'bathroom privileges') for at least 3 days with an acute illness.
- Cesarean section.

Minor (yet important) transient risk factor during the 2 months before diagnosis of VTE

- Surgery with general anesthesia for less than 30 min.
- Admission to hospital for less than 3 days with an acute illness.
- Estrogen therapy.
- Pregnancy or puerperium.
- Confined to bed out of hospital for at least 3 days with an acute illness.
- Leg injury associated with reduced mobility for at least 3 days.

VTE PROVOKED BY A PERSISTENT RISK FACTOR

e.g

Active cancer

Inflammatory Bowel Disease

Obesity

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Practical Approaches

1. Provoking Factors

2. Bleeding Risk

3. Bleeding risk calculators e.g. HASBLED

4. Recurrence Prediction Scores using D-Dimer off treatment

e.g. DASH

Recurrence Risk vs Bleeding Risk

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DASH/HERDOO

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Rate of venous thromboembolism (VTE) recurrence

	First year
	10 percent
	15 percent
	1 percent
r	5 percent

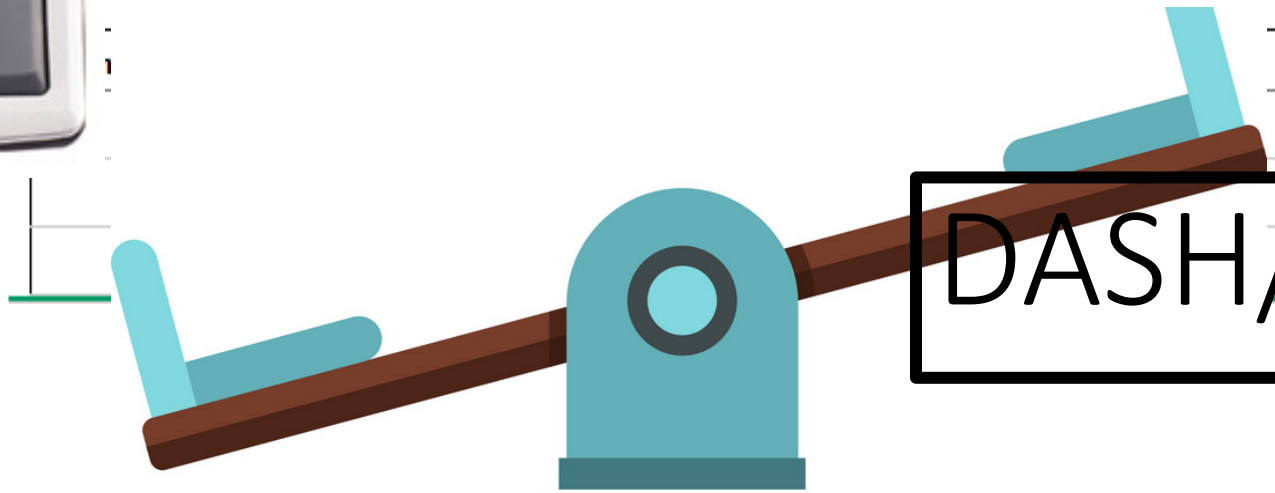
Equation

Variable

$$2x - 3^2 = 10x$$

Expression — Coefficient — Term

≥2.5
≥4
≥6.



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Rate of venous thromboembolism (VTE) recurrence

Equation	First year
	10 percent
	15 percent
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	≥2.5
	≥4
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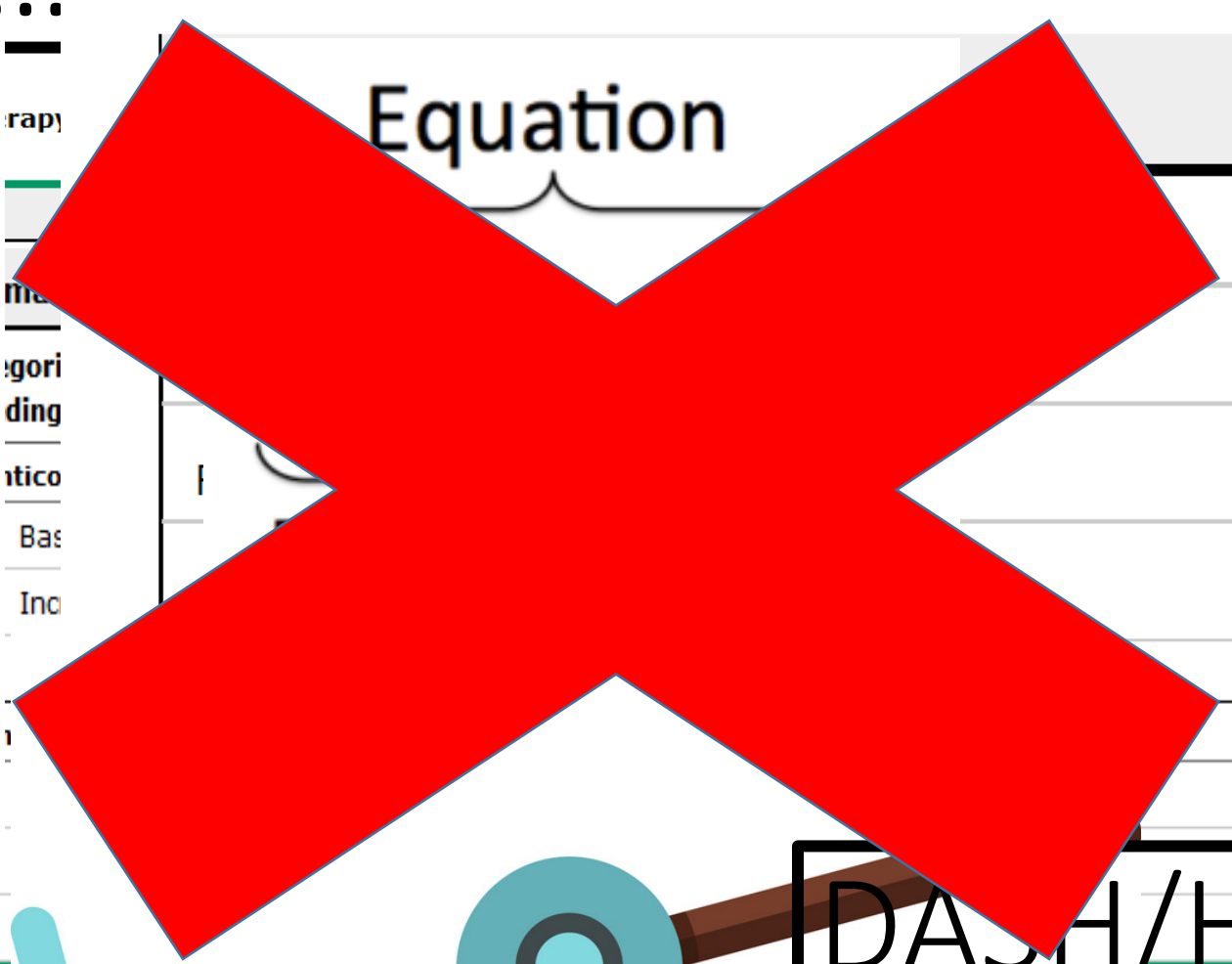

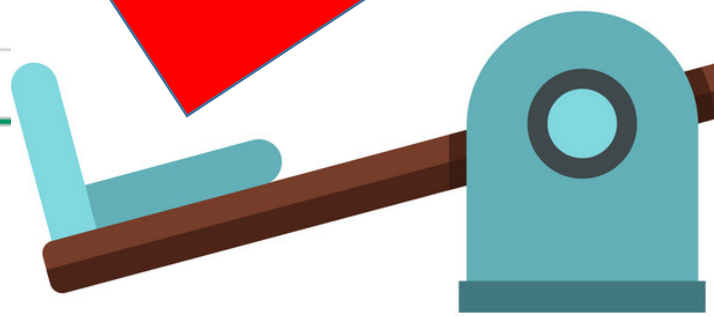

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STOP	---------?---------	KEEP GOING
HIGH BLEEDING RISK AND NOT RECURRENT	RECURRENT PROVOKED VTE	UNPROVOKED VTE AND NOT HIGH BLEEDING RISK
BELOW KNEE DVT	UNPROVOKED WITH PATIENT PREFERENCE AGAINST CONTINUING	RECURRENT UNPROVOKED VTE
VTE DUE TO PROVOKING FACTOR WHICH IS REVERSED	PROVOKED VTE WITH PERSISTENT RISK FACTOR (CONTINUE UNTIL REVERSED);	CANCER
HORMONE RELATED THROMBOSIS	PROVOKING FACTOR UNCLEAR	OTHERS: APLS, MPN, PNH
	RECURRENT UNPROVOKED AND HIGH BLEEDING RISK	

Practical Approaches

1. Provoking Factors – RECURRENCE RISK

2. Bleeding Risk

3. Patient Factors

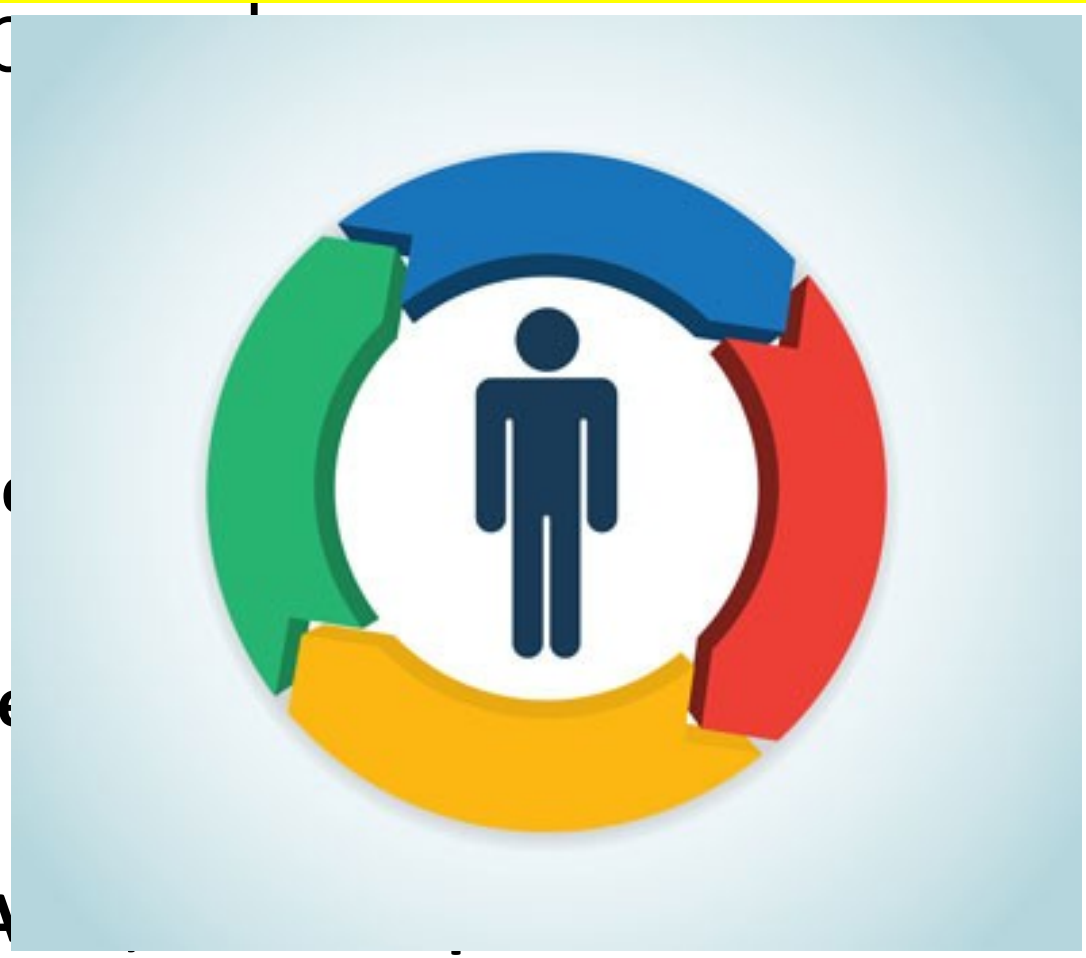
- **Preferences, activities, occupation**
- **co-morbidities**
- **impact of recurrence e.g. lung disease&PE**
- **Impact of bleeding**

4. Additional tests ~~– Thrombophilia screens,~~ APLS

5. Clinical Rules – not routinely (not prospectively validated, not featured in guidelines)

INDIVIDUAL PATIENT CENTERED APPROACH

Practical App



1. **Provoking Factors**
2. **Bleeding Risk**
3. **Patient Factors**
   - **Preferences, activiti**
   - **co-morbidities**
   - **impact of recurrenc**
   - **Impact of bleeding**
4. **Additional tests – A**
5. **Clinical Rules – not routine**

Guidelines

	International Consensus Statement International Union Angiology 2013	ISTH Guidance 2012	ACCP Guidelines 2016	NICE GUIDELINES
Transient Major Provoking Factor	3months then stop	3months then stop	Recommend 3 months over a shorter period or 6,12,24 months	3 months
Transient Minor Provoking Factor	Assess to consider indefinite			

Guidelines

	International Consensus Statement International Union Angiology 2013	ISTH Guidance 2012	ACCP Guidelines 2016	NICE GUIDELINES
Unprovoked VTE	Assess to consider indefinite	Assess to consider indefinite	Extended therapy (no scheduled stop date) if low or moderate bleeding risk	Offer a vitamin K antagonist beyond 3 months to patients with an unprovoked PE, taking into account the patient's risk of VTE recurrence and whether they are at increased risk of bleeding.
Unprovoked Calf DVT		3 months then stop	Recommend 3 months over a shorter period or 6,12,24 months. Unless no severe symptoms, no risk factors for extension or high risk of bleeding (serial imaging)	
Upper Limb Thrombosis		3months only unless indwelling central venous catheter, persistent thoracic outlet syndrome or severe postthrombotic syndrome.		

Guidelines

	International Consensus Statement International Union Angiology 2013	ISTH Guidance 2012	ACCP Guidelines 2016	NICE GUIDELINES
>1 VTE	Indefinite		Extended therapy (no scheduled stop date) if low or moderate bleeding risk	
Hormone (estrogen) Associated VTE		3 months then stop	Recommend 3 months over a shorter period or 6,12,24 months	

	International Consensus Statement International Union Angiology 2013	ISTH Guidance 2012	ACCP Guidelines 2016	NICE GUIDELINES
Use of D-Dimer/sex to guide	Data insufficient	May favour indefinite anticoagulation	No recommendation/uncertainty	
Use of Residual DVT on imaging to guide	Data insufficient	Not clinically useful		
Thrombophilia Testing		Not recommended		Consider testing for antiphospholipid antibodies in patients who have had unprovoked DVT or PE if it is planned to stop anticoagulation treatment. Consider testing for hereditary thrombophilia in patients who have had unprovoked DVT or PE and who have a first-degree relative who has had DVT or PE if it is planned to stop anticoagulation treatment.

QUIZ 5 Questions

Disclaimer: 2 dimensional cases/opinions may differ…!

1/5: A 48 yr old female on COCP since 18 years. eczema, BMI 35, hypothyroid, Crohn’s disease, not high bleeding risk

A.6 weeks

B.3 months only

C.6months only

D.Indefinite

2/5: A 50 year old male with an unprovoked DVT in gastrocnemius vein and deemed to have low bleeding risk

A.6 weeks

B.3 months only

C.6months only

D.Indefinite

3/5: A 67 yr old female with hospital acquired PE, COPD, frequent admissions with chest infection, not high bleeding risk

A.6 weeks

B.3 months only

C.6months only

D.Indefinite

4/5: A 58 yr old female with thrombosis of great saphenous vein, no provoking factors, low bleeding risk

A.6 weeks

B.3 months only

C.6months only

D.Indefinite

5/5: A 72 yr old female with unprovoked proximal DVT, Obesity, previous cerebral bleed and cerebral amyloid angiopathy

A.6 weeks

B.3 months only

C.6months only

D.Indefinite

Thank-you