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BACKGROUND

International Normalized Ratio (INR) is a measure of the ability of blood to clot properly. Excessive INR response to vitamin K antagonist (VKA) anticoagulant therapy is associated with increased risk of hemorrhage and bleeding disorder [1]. Table 1 lists the recommended therapeutic ranges of INR for common indications:

Table 1: Recommended therapeutic ranges of the international normalized ratio (INR) for common indications for oral anticoagulant therapy*

Indication	INR range
Prophylaxis of venous thrombosis (high-risk surgery)	2.0–3.0
Treatment of venous thrombosis	
Most cases of thrombosis with antiphospholipid antibody syndrome[7]	
Treatment of pulmonary embolism	
Prevention of systemic embolism	
Tissue heart valves	
AMI (to prevent systemic embolism)	
Valvular heart disease	
Atrial fibrillation	
Bileaflet mechanical valve in aortic position	
Mechanical prosthetic valves (high risk)	2.5–3.5
Prophylaxis of recurrent myocardial infarction	

*Adapted, with permission, from Hirsh et al.[8]

Patients receiving long term VKA anticoagulant therapy are above the therapeutic INR range from 14-30% of the time [2, 3]. Over anticoagulation is thus a common clinical problem [3]. Patients are at a high risk of bleeding when INR levels are greater than 4-4.5, and thus there is a need to reduce INR levels [1]. Fatal hemorrhage occurs in 0.1-1% of patients, serious permanent morbidity in 3-10% of patients, and up to 25% of patients experience at least 1 minor bleed annually [4]. Studies were compiled on the treatment of elevated INR values with vitamin K_1 therapy [1-6].

FINDINGS

Vitamin K_1 is administered both orally and by injection. The efficacy of the different administration routes is comparable; both have a similar effect on INR [1]. However, there is a difference in the rate of reversal of anticoagulation between intravenous vitamin K and oral vitamin K [1, 3]. Oral vitamin K (injectable formulation given orally) has a 4 hour lag time between administration and effect, but does produce therapeutic INR values in 24 hours [2].

Injectable vitamin K presents several problems. Vitamin K has been associated with reports of severe anaphylactic and anaphylactoid reactions after intravenous administration, and also local adverse

effects at intramuscular and subcutaneous sites [5]. Two types of reactions were found: pruritic, indurated, eczematous plaques developing 4-14 days post injection lasting up to several months; sclerodermoid lesions (Texier's disease) which begins with weeks to months after injection and may persist for years [5].

For patients with asymptomatic elevated INR oral vitamin K is the preferred route of administration [1-6]. Oral is favoured over intravenous because the response to vitamin K is more predictable and oral administration is easier [1]**.** A study conducted by Watson et al. compared 3 different forms of oral vitamin K (1 mg capsule, 5 mg tablet, 2 mg and 5 mg injectable formulations given orally); they found that only the injectable product given orally produced a predictable and effective lowering of INR levels after 24 hours [3]. Therefore, the different oral vitamin K formulations do indeed have different efficacy [3]. If indicated at all, the dose of oral vitamin K therapy for patients with elevated INR (4.5-10) is generally agreed to be 1.0 mg [2, 6]. Dosing of 2.0 mg for patients with INR 4.5-10 resulted in 33% of patients with an INR below therapeutic range (INR<2), compared to 0-16% of patients receiving 1.0 mg vitamin K [2]. For INR ≥10, current Chest guidelines suggest initiating therapy at a higher oral dose of vitamin K (2.5mg). In patients that have sustained serious bleeding, sending the patient to the closest Emergency Room is appropriate (see appendix 1).[7]

SUMMARY AND RECOMMENDATIONS

Routine use of vitamin K for INRs between 5 and 9 is not recommended by the Calgary Zone Anticoagulation Management Services guidelines. If warranted (e.g. rapid reversal required), low dose vitamin K 1 – 5 mg given orally may be appropriate. In patients with INR values greater than 9 and without serious bleeding, 2.5 – 5 mg of vitamin K given orally is appropriate. If the patient has serious bleeding at any elevation of INR, vitamin K 10 mg by slow IV infusion is recommended.

See **Appendix 1** for Recommendations for Managing Elevated INRs or Bleeding in Patients Receiving Vitamin K Antagonists in Long Term Care.

See **Appendix 2** for the Calgary Zone AMS Assessment Nomogram for Supra-therapeutic INRs

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Appendix 1

*Recommendations for Managing Elevated INRs or Bleeding in Patients Receiving Vitamin K Antagonists in Long Term Care **

(Adapted from Calgary Zone AMS Guidelines for Correction of Over-anticoagulation (May 2015))

INR	Clinical Setting	Therapeutic Options
> Target < 5.0	No significant bleeding	Reduce warfarin dose **OR** Omit warfarin dose x 1, restart at lower dose Recheck INR in 1 – 7 days Note: if only minimally above target range, no dose reduction may be required.
5.0 - 9.0*	No significant bleeding	Omit warfarin x 1- 2 doses, restart at lower dose; recheck INR in 2 days Recheck CBC in 2 day in patients with new minor bleeding or high bleed risk¶ Notify MD. If resident is on protocol, protocol is discontinued.
5.0 – 9.0	Rapid reversal required (i.e. urgent surgery)	Hold warfarin Notify MD Vitamin K_1 1 – 5 mg PO (↓ INR within 24 hours) Repeat vitamin K_1 1 – 2 mg PO if remains elevated Recheck INR in 1 day (or a.m. of pre-op day)
5.0 – 9.0	Serious bleeding	Hold warfarin, call EMS to transport to ED Notify MD Use management strategies for INR > 9.0 (see below) after appropriate assessment of bleeding
> 9.0**	No significant bleeding	Hold warfarin until INR in target range Notify MD **Any time INR >9.0** patient to have 2.5 - 5 mg vitamin K_1 PO; recheck CBC and INR in 1 day¶ Give repeat doses vitamin K_1 2.5 - 5 mg PO (↓ INR in 24 – 48 hrs) as needed.
> 9.0	Serious bleeding	Hold warfarin, call EMS to transport to ED Notify MD Vitamin K_1 10 mg slow IV infusion per EMS/ED protocols ↓ INR in 6 – 8 hours May repeat q12h Additional Reversal Products as per ED Protocol
> 9.0	Life threatening bleeding	Hold warfarin, call EMS to transport to ED Notify MD Give Vitamin K_1 10 mg slow IV infusion per EMS/ED protocols and repeat if needed. Additional Reversal Products as per ED Protocol; consult Hematology

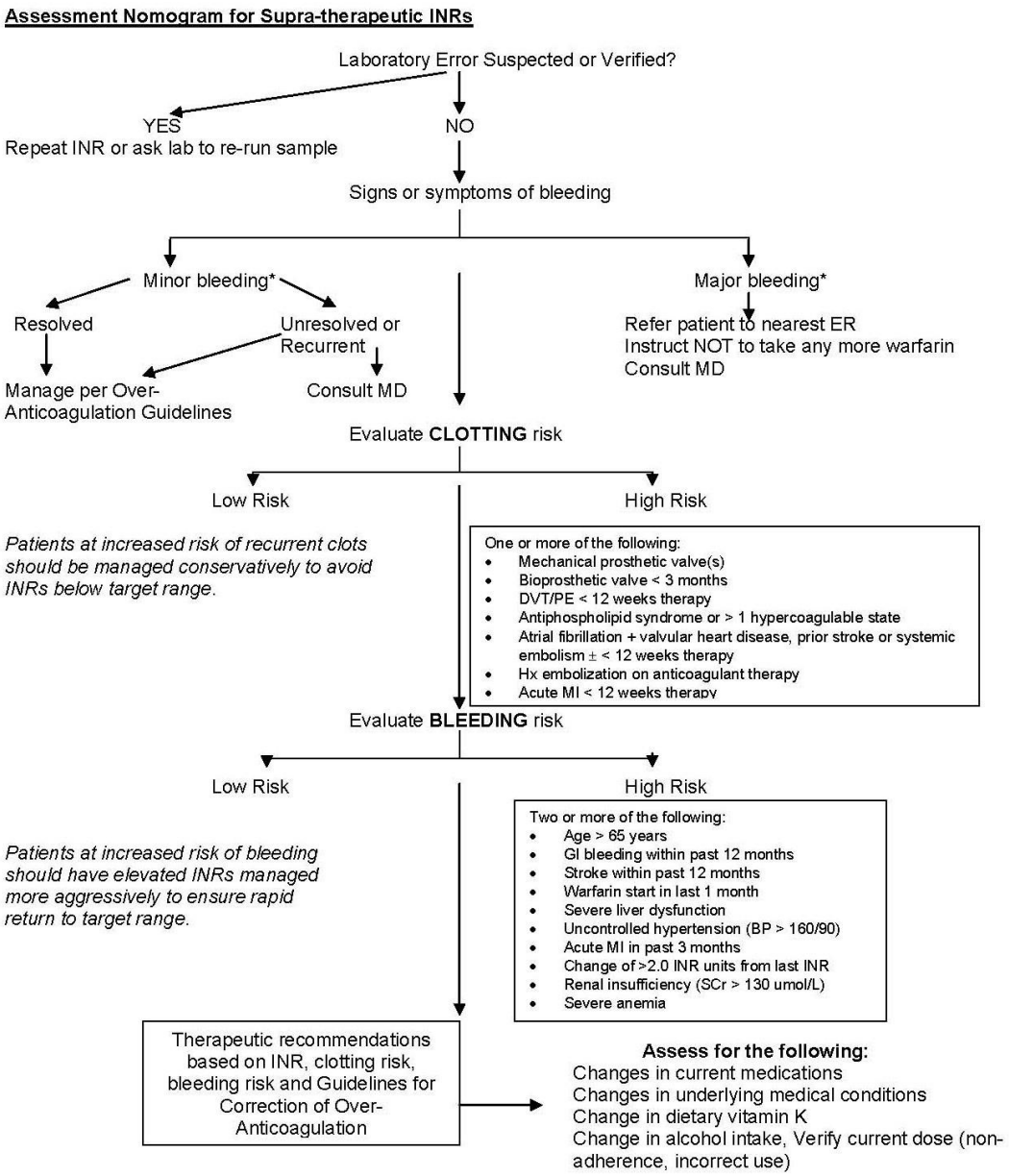
¶ Management strategy for patients with high bleeding risk.

*For INR 5.0 – 9.0: Although vitamin K use in patients without bleeding may reverse supratherapeutic INRs more rapidly versus only withholding VKA , there is no evidence of benefit for patient-important outcomes (rates of major bleeding and thromboembolism).

**For INR > 9.0 without bleeding: Patient preferences and clinical assessment of risks of thrombosis and bleeding are likely important factors in determining whether to give vitamin K. The benefit and harm of vitamin K administration for patients with an INR >9.0 and no bleeding are unclear, although the risk of bleeding may be substantial.

Appendix 2

Calgary Zone AMS Assessment Nomogram for Supra-therapeutic INRs



***Major bleeding**: any overt bleeding that results in hospitalization, transfusion, or a decrease in HgB ≥ 20 g/L, any intracranial, intraocular, or retroperitoneal bleeding, and any bleeding resulting in death.*
***Minor bleeding**: bleeding that can be managed on an outpatient basis, e.g. mild nosebleeds, bruising, mild hemorrhoidal bleeding, and microscopic hematuria.*
2002.

Clinical Practice Guidelines are developed to assist in care and treatment decisions and are intended to be used with clinical judgment.