Management of Subtherapeutic and Supratherapeutic INR Values

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Faculty/Presenter Disclosure

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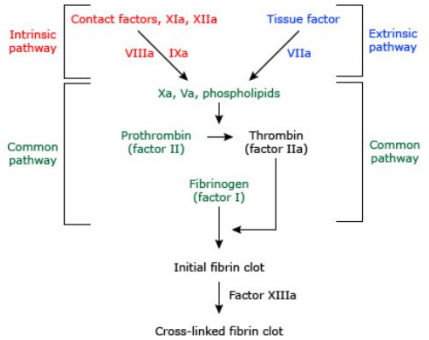
Objectives

1. Understand therapeutic lag with warfarin
2. Manage warfarin dosing when INR sub/supratherapeutic or during warfarin initiation
3. Monitor INR appropriately during dose changes/INR excursions and when starting/stopping interacting medications
4. Manage warfarin/anticoagulation intraoperatively

Background:

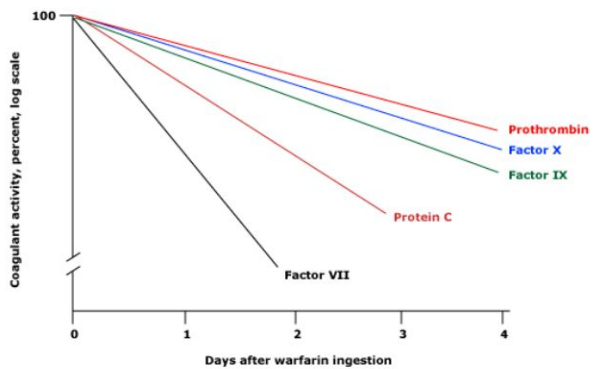
Warfarin is an indirect anticoagulant producing its effect by decreasing the ability of the liver to produce fully functional coagulation factors II, VII, IX, and X, as well as the endogenous anticoagulants, protein C and protein S.

Intrinsic, extrinsic, and common coagulation pathways



Schematic representation of the intrinsic (red), extrinsic (blue), and common (green) coagulation pathways. Contact factors include prekallikrein and HMWK. In the clinical laboratory, the intrinsic (and common) pathway is assessed by the aPTT and the extrinsic (and common) pathway by the PT. The TT assesses the final step in the common pathway, the conversion of fibrinogen to fibrin, following the addition of exogenous thrombin. Fibrin is crosslinked through the action of factor XIII, making the final fibrin clot insoluble in 5 Molar urea or monochloroacetic acid. This latter function is not tested by the PT, aPTT, or TT.

Effect of warfarin on blood clotting proteins



The activity of various clotting proteins (logarithmic scale) is shown here as a function of time after ingestion of warfarin (10 mg/day PO for four consecutive days) by a normal subject. Factor VII activity, to which the prothrombin time is most sensitive, is the first to decrease. Full anticoagulation, however, does not occur until factors IX, X, and prothrombin are sufficiently reduced. Protein C activity falls quickly, and, in some patients, a transient hypercoagulable state may ensue (eg, coumarin necrosis).

Case #1

Edna, a 54-year-old female has been diagnosed with a pulmonary embolism. She has a history of epilepsy, which is well controlled with phenytoin. She also takes ramipril for hypertension, rosuvastatin for dyslipidemia, and a baby aspirin daily.

Q1) What is an appropriate oral anticoagulant for this patient?

Q2) What would you choose as a starting dose?

Q3) When would you check INR?

Q4) Does she require bridging with LMWH?

Options for initial anticoagulation include direct acting oral anticoagulant (DOAC) monotherapy (for apixaban and rivaroxaban), unfractionated heparin (UFH) or low molecular weight heparin (LMWH) initial therapy followed by DOAC (for dabigatran and edoxaban), LMWH/UFH bridging to therapeutic warfarin, or LMWH monotherapy (**Figure 1**). Recent guideline recommendations express a preference for DOAC therapy over LMWH bridging to warfarin. While both strategies are effective, DOACs are more convenient and appear to have lower bleeding risk. The extent of PE or clot burden should not influence choice of anticoagulant, unless thrombolysis is being considered; in that case, intravenous (IV) UFH is preferred in the short-term due to its short half-life in the context of the bleeding risk associated with thrombolysis. All patients with PE should be treated with anticoagulation for at least 3 months [see **Clinical Guide Venous Thromboembolism: Duration of Treatment** guide].

Lexicomp: Interactions

Apixaban / Inducers of CYP3A4 (Strong) and P-glycoprotein

Risk Rating X: Avoid combination

Summary Inducers of CYP3A4 (Strong) and P-glycoprotein may decrease the serum concentration of Apixaban. Severity Major Reliability Rating Good

Patient Management Avoid concurrent use of apixaban with drugs that are strong CYP3A4 inducers and P-gp inducers.

Inducers of CYP3A4 (Strong) and P-glycoprotein Interacting Members Apalutamide, CarBAMazepine, Fosphenytoin, Phenytoin, RifAMPin

Patients expected to be **more** sensitive to warfarin include adults who are: frail, elderly, or undernourished; have liver disease, kidney disease, heart failure, or acute illness; or are receiving a medication known to decrease warfarin metabolism

Further dose changes can be made using validated maintenance nomogram

Minimum 5 days overlap with LMWH with at least 2 consecutive therapeutic INR values

Example Warfarin Initiation Nomogram Targeting an INR Range of 2 to 3 (for Outpatients or Clinically Stable Inpatients) (Adapted From Wittkowsky 2018)[a]

	Standard dosing for patients who are *not* expected to be sensitive to warfarin[b]	**Reduced dosing for patients expected to be more sensitive to warfarin[c]**
Initial dose	5 mg daily for 3 days[d]	2.5 mg daily for 3 days
Check INR the morning of day 4		
<1.5	7.5 to 10 mg daily for 2 to 3 days	5 to 7.5 mg daily for 2 to 3 days
1.5 to 1.9	5 mg daily for 2 to 3 days	2.5 mg daily for 2 to 3 days
2 to 3	2.5 mg daily for 2 to 3 days	1.25 mg daily for 2 to 3 days
3.1 to 4	1.25 mg daily for 2 to 3 days	0.5 mg daily for 2 to 3 days
>4	Hold until INR <3	Hold until INR <3

[a]Dosing nomograms offer a reasonable starting point for estimating an initial warfarin dose and subsequent adjustments but should not serve as a substitute for clinical judgment. If the patient received warfarin previously, history of prior dose requirement is useful for guiding reinitiation of therapy.

RxFiles is a great resource for locating this information!

WARFARIN TIPS & DOSING NOMOGRAMS

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Warfarin has been used for over 60 years & is approved for multiple indications e.g. stroke prevention in atrial fibrillation, heart valve disease/replacement, venous thromboembolism prophylaxis & treatment, post-myocardial infarction/acute coronary syndrome, etc. When appropriately managed in compliant stable patients, warfarin is safe & effective safety & effectiveness ↑ as time in therapeutic range ↑.

MANAGEMENT PEARLS

- Use a validated nomogram for initiating & maintaining warfarin. Nomograms have been shown to ↑ time in therapeutic range (TTR) see Tables 1, 2 & 3.[CADTH, CHEST '16, 3]
- Extend the frequency of international normalized ratio (INR) monitoring to q12wks in pts who have had stable INRs for ≥3 mos,[CHEST'16] ensure pt will report any drug changes between INRs.
- In pts maintained on warfarin, do not adjust dose based on an asymptomatic, single, unexplained e.g. no drug/dietary Δ, out-of-range INR **≤0.5 ± target range**; recheck in 1-2 wks.[2,4]
- If concomitant use of a drug that alters INR cannot be avoided, ↑ INR monitoring & reactively (**not** proactively) adjust the dose in response, except if can predict response based on past DI.

INITIATING WARFARIN see Tables 1 & 2 (SAMe-TT$_2$R$_2$ score: help choose between warfarin or DOAC[Chest'18])

- Collect INR on Day 1 **only if** no baseline available; INR on Day 2 *usually* not needed.
- **Target INR** - for most: **2.5** (acceptable range = **2 - 3**)
  - for mechanical mitral valve replacement: **3** (acceptable range **2.5 - 3.5**)
- Consider dispensing in strengths that accommodate dose changes e.g. 1 & 2mg, 1 & 5mg.
- Use one of the following regimens **when starting** warfarin; consider the patient's risk factors for clotting or extension of existing clot & bleeding:[5,6]

Option 1: Warf 2-3mg x 2 days Elderly, high bleed risk, etc

1) Warfarin 2-3mg po daily x 2 days, Day 3 INR, subsequent doses based on INRs

- Consider in pts who may be more sensitive to warfarin, e.g. **elderly, debilitated, malnourished, HF, liver dx, ↑ risk of bleeds or taking medications known to ↑ INR.**
- There is no validated nomogram for this regimen, but can use same % ↑ or ↓ as outlined in Table 1 (e.g. 3mg Day 1 & 2, with a Day 3 INR of <1.5→ give either 3mg or 6mg).

Option 2: Warf 5mg x 2 days Most commonly used

2) Warfarin 5mg po daily x 2 days, Day 3 INR, subsequent doses based on INRs

TABLE 1: INITIATING WARFARIN - EXAMPLE OF A VALIDATED NOMOGRAM FOR 5mg DAY 1 & DAY 2 (INR 2-3)[6]

DAY 3		DAY 4 (OPTIONAL INR)		DAY 5		DAY 6 (OPTIONAL INR)	
INR	DOSE(mg)	INR	DOSE(mg)	INR	DOSE (mg)	INR	DOSE (mg)
< 1.5	5 – 10	< 1.5	10	< 1.5	10	< 1.5	7.5 – 12.5
1.5 – 1.9	2.5 – 5	1.5 – 1.9	5 – 7.5	1.5 – 1.9	7.5 – 10	1.5 – 1.9	5 – 10
2 – 3	0 – 2.5	2 – 3	0 – 5	2 – 3	0 – 5	2 – 3	0 – 7.5
> 3	0	> 3	0	> 3	0	> 3	0

3) Warfarin 10mg po daily x 2 days, Day 3 INR, subsequent doses based on INRs

Option 3: Warf 10mg x 2 days Younger, low bleed risk patients

TABLE 2: INITIATING WARFARIN - VALIDATED NOMOGRAM FOR 10MG DAY 1 & DAY 2 (INR 2-3)[7]

Warfarin 10mg x Day 1 & Day 2:
- likely safe & effective for **outpatients not at high risk of bleeding** [CHEST'12]
- may achieve therapeutic INR faster [7]

DAY 3 INR	DAY 3 & 4 DOSE (mg)	DAY 5 INR	DAY 5, 6 & 7 DOSE (mg)
<1.3	15, 15	< 2	15, 15, 15
		2 – 3	7.5, 5, 7.5
1.3 - 1.4	10, 10	3.1 – 3. 5	0, 5, 5
		> 3.5	0, 0, 2.5
1.5 - 1.6	10, 5	< 2	7.5, 7.5, 7.5
		2 – 3	5, 5, 5
1.7 – 1.9	5, 5	3.1 – 3.5	2.5, 2.5, 2.5
		> 3.5	0, 2.5, 2.5
2 – 2.2	2.5, 2.5	< 2	5, 5, 5
		2 – 3	2.5, 5, 2.5
2.3 – 3	0, 2.5	3.1 – 3.5	0, 2.5, 0
		> 3.5	0, 0, 2.5
>3	0, 0	< 2	2.5, 2.5, 2.5
		2 – 3	2.5, 0, 2.5
		3.1 – 4	0, 2.5, 0
		> 4	0, 0, 2.5

FREQUENCY OF INR MONITORING

- **Initiating warfarin**: see 3 options/examples to the left; in general, week 1: Baseline, Day 3 & 5, week 2: 2 INRs, then weekly INRs until stable x 2 weeks, then q2weeks until stable x 1 month, then monthly INRs. If stable x 3 months → INR up to q12 weeks,[CHEST'12] ensure patient will report any changes in drug therapy between INRs.
- **Warfarin dose changes**: check INR weekly until stable.
- **Starting, stopping or changing the dose of an interacting drug**: check INR in 4-6 days after the change. ↑ Monitoring duration for drugs with long t½ or onset e.g. amiodarone.

MANAGEMENT OF SUB-/SUPRATHERAPEUTIC INRS see Figure & Table 3

- Interpretation of INR requires many considerations:
  - trend & time since last INR, duration of current dose full therapeutic effect may take 5-7 days
  - changes in medications (starting, stopping & changes in doses) of interacting medications, see Managing Warfarin Drug Interactions on the next page
  - factors that may ↑ INR: acute illnesses e.g. diarrhea, fever, ↑ in alcohol intake
  - factors that may ↓ INR: edema, ↑ vitamin K intake (e.g. garden harvest), ↑ physical activity level
  - patients with heart failure, diabetes & acute GI illness may experience INR instability.[8]

FIGURE: STEPWISE APPROACH FOR SUB-/SUPRATHERAPEUTIC INRS

Step 1: Note indication for warfarin & target INR. **Is the patient symptomatic for the INR?**
- If INR high, are there signs/symptoms of bleeding? Consider risk (platelet count, bleeding disorders)!
- If INR is low, are there signs &/or symptoms of a stroke or VTE?

If **yes**, provide appropriate emergent/urgent care. If **no**, proceed to Step 2.

Step 2: Is the patient at risk of becoming symptomatic for the INR?
- If the INR >10: hold warfarin, & give vitamin K 2.5-5mg ampule po x1. {ACC'20: major bleed: Vit K 5-10mg IV & consider 4F-PCC; non-major bleed: Vit K 2-5mg po/IV} ↓ weekly warfarin dose by 20% & resume once INR in therapeutic range. Re-check INR in ~2 days. Next day INR will likely still be elevated. Avoid IM vitamin K.
- If the INR is low, consider bridging with LMWH if the patient is at high risk of a clot.

Step 3: Identify if sub-/supratherapeutic INR is a result of a permanent or transient cause.
- **Transient causes**: e.g. missed/extra dose, gastroenteritis, course of antibiotics, recent ↑ alcohol intake
  - Consider dose correction e.g. hold or give extra dose & ↑ INR monitoring frequency
- **Permanent causes**: e.g. lifestyle change, change with a chronic medication
  - Consider a change in weekly dose see Table 3 below & ↑ INR monitoring frequency

- Vitamin K 100-200 mcg po daily may help stabilize INR in pts with unexplained fluctuating INRs, but lacks evidence for routine use. Tablets are available at health food stores (e.g. GNC).
- High vitamin K doses can cause warfarin resistance for ~1 week.

TABLE 3: MAINTENANCE OF WARFARIN – EXAMPLE VALIDATED NOMOGRAM[9]

TARGET INR 2 – 3	ACTION	TARGET INR 2.5-3.5
< 1.5	Extra dose, ↑ weekly dose by 10-20%	< 2
1.5 – 1.9	↑ weekly dose by 5-10%	2 – 2.4
2 – 3	No Change	2.5 – 3.5
3.1 – 3.5	↓ weekly dose by 5-10%	3.6 – 4
3.6 – 4.9	Hold 1 dose, ↓ weekly dose by 10-20%	4.1 – 4.9
5 – 9	Hold 2 doses, ↓ weekly dose by 10-20%	5 – 9
> 9	Urgent evaluation	> 9

Do not adjust warfarin dose based on 1 **asymptomatic, unexplained,** out-of-range maintenance INR **≤0.5 ± target range.** Recheck INR in 1-2 **wks.**

n 2: Warf 5mg x 2 days
ost commonly used

2) Warfarin 5mg po daily x 2 days, Day 3 INR, subsequent doses based on INRs

TABLE 1: INITIATING WARFARIN - EXAMPLE OF A VALIDATED NOMOGRAM FOR 5mg DAY 1 & DAY 2 (INR 2-3)[6]

DAY 3		DAY 4 (OPTIONAL INR)		DAY 5		DAY 6 (OPTIONAL INR)	
INR	DOSE(mg)	INR	DOSE(mg)	INR	DOSE (mg)	INR	DOSE (mg)
< 1.5	5 – 10	< 1.5	10	< 1.5	10	< 1.5	7.5 – 12.5
1.5 – 1.9	2.5 – 5	1.5 – 1.9	5 – 7.5	1.5 – 1.9	7.5 – 10	1.5 – 1.9	5 – 10
2 – 3	0 – 2.5	2 – 3	0 – 5	2 – 3	0 – 5	2 – 3	0 – 7.5
> 3	0	> 3	0	> 3	0	> 3	0

Option 3: Warf 10mg x 2 days Younger, low bleed risk patients

TABLE 2: INITIATING WARFARIN - VALIDATED NOMOGRAM FOR 10MG DAY 1 & DAY 2 (INR 2-3) [7]

Warfarin 10mg x Day 1 & Day 2:

- likely safe & effective for **outpatients not at high risk of bleeding** CHEST'12
- may achieve therapeutic INR faster [7]

DAY 3 INR	DAY 3 & 4 DOSE (mg)	DAY 5 INR	DAY 5, 6 & 7 DOSE (mg)
<1.3	15, 15	< 2	15, 15, 15
		2 – 3	7.5, 5, 7.5
1.3 - 1.4	10, 10	3.1 – 3. 5	0, 5, 5
		> 3.5	0, 0, 2.5
1.5 - 1.6	10, 5	< 2	7.5, 7.5, 7.5
		2 – 3	5, 5, 5
1.7 – 1.9	5, 5	3.1 – 3.5	2.5, 2.5, 2.5
		> 3.5	0, 2.5, 2.5
2 – 2.2	2.5, 2.5	< 2	5, 5, 5
		2 – 3	2.5, 5, 2.5
2.3 – 3	0, 2.5	3.1 – 3.5	0, 2.5, 0
		> 3.5	0, 0, 2.5
>3	0, 0	< 2	2.5, 2.5, 2.5
		2 – 3	2.5, 0, 2.5
		3.1 – 4	0, 2.5, 0
		> 4	0, 0, 2.5

NORTHERN HEALTH REGION

WARFARIN INITIATION GUIDELINES

These guidelines were developed and provided from the thrombosis service at McMaster University, Hamilton Health Sciences and Rx Files.

The physician must indicate protocol desired, this includes the physician's signature.

☐ _____ Signature

☐ _____ Signature

☐ _____ Signature

Not sensitive patients starting on Warfarin		
Day	**INR**	**warfarin dose, mg**
1 and 2		**10**
3	**Less than 1.5**	**15**
	1.5 – 2.0	**10**
	2.1 – 3.0	**5**
	3.1 – 3.5	**2.5**
	More than 3.5	**0**
4	**Less than 1.5**	**15**
	1.5 – 2.0	**10**
	2.1 – 2.5	**7.5**
	2.6 – 3.0	**5**
	3.1 – 3.5	**2.5**
	More than 3.5	**0**

For:

- Young patients

Moderately sensitive patients starting on Warfarin		
Day	**INR**	**warfarin dose, mg**
1 and 2		**5**
3	**Less than 1.5**	**10**
	1.5 – 2.0	**5**
	2.1 – 3.0	**2.5**
	More than 3.0	**0**
4	**Less than 1.5**	**10**
	1.5 – 2.0	**7.5**
	2.1 – 3.0	**5**
	More than 3.0	**0**
5	**Less than 1.5**	**12.5**
	1.5 – 2.0	**10**
	2.1 – 2.5	**7.5**
	2.6 – 3.0	**5**
	More than 3.0	**0**
6	**Less than 1.5**	**15**
	1.5 – 2.0	**12.5**
	2.1 – 3.0	**7.5**
	3.1 – 3.5	**2.5**
	More than 3.5	**0**

For:

- Usual dosing

Very sensitive patients starting on Warfarin		
Day	**INR**	**warfarin dose, mg**
1 and 2		**2.5**
3	**Less than 1.5**	**5**
	1.5 – 2.0	**2.5**
	2.1 – 3.0	**1**
	More than 3.0	**0**
4	**Less than 1.5**	**7.5**
	1.5 – 2.0	**5**
	2.1 – 3.0	**2.5**
	More than 3.0	**0**
5	**Less than 1.5**	**10**
	1.5 – 2.0	**7.5**
	2.1 – 3.0	**5**
	3.1 – 4.0	**2.5**
	More than 4.0	**0**

For:

- Old patients
- Multiple drug interactions

****In case of high INR resulting in a dose of 0mg, subsequent dosing must be individualized.**

Thrombosis Canada
Thrombose Canada

Warfarin

Initiation of warfarin should be combined with an immediate-acting agent such as LMWH for at least 5 days and until the international normalized ratio (INR) is at least 2.0 for at least 2 days. As warfarin takes several days to take effect, warfarin monotherapy is not an acceptable treatment option.

Bridge

Case #1

Edna, a 54-year-old female has been diagnosed with a pulmonary embolism. She has a history of epilepsy, which is well controlled with phenytoin. She also takes ramipril for hypertension, rosuvastatin for dyslipidemia, and a baby aspirin daily.

Q1) What is an appropriate oral anticoagulant for this patient? Warfarin

Q2) What would you choose as a starting dose? 5mg PO daily

Q3) When would you recheck INR? Day 3-7 as directed by nomogram

Q4) Does she require bridging with LMWH? Yes

Stop the ASA!!!

Case #2

Alfred is a 65-year-old male with a a mechanical aortic valve (2015, bi-leaflet). He also has CHF, HTN, and BPH. His medications are as follows:

- Warfarin 4mg PO daily
- Metoprolol 100mg PO BID
- Ramipril 10mg PO BID
- Furosemide 40mg PO daily
- Spironolactone 25 PO daily
- Tamsulosin 0.4mg PO daily

He recently had blood work and his INR value was 1.8. He has not started or changed any of his medications recently. His previous 2 INR values were in the normal range.

Q1) Would you adjust the dose?

Q2) When would you recheck INR?

Managing Single Out-of-Range INR Values

For patients with previously in-range INR values who present with a single slightly out-of-range INR (e.g. INR 0.5 above or below the target range), there are two management options

1. **Continue current maintenance dose and repeat INR in 1-2 weeks**

OR

2. **Make a one-time dose change (increase or hold by ½ to 1 single dose) and resume current maintenance dose. Repeat INR in 1-2 weeks.**

The specific approach is influenced by the magnitude of the out-of-range value, previous experience of similar values in the patient and whether the patient has strong risk factors for thrombosis/stroke or bleeding.

Case #2

Alfred is a 65-year-old male with a history of a mechanical aortic valve (2015, bi-leaflet). He also has CHF, HTN, and PPH. His medications are as follows:

- Warfarin 4mg PO daily
- Metoprolol 100mg PO BID
- Ramipril 10mg PO BID
- Furosemide 40mg PO daily
- Spironolactone 25 PO daily
- Tamsulosin 0.4mg PO daily

He recently had blood work and his INR value was 1.8. He has not started or changed any of his medications recently. His previous 2 INR values were in the normal range.

Q1) Would you adjust the dose?

No

Q2) When would you recheck INR?

1-2 weeks

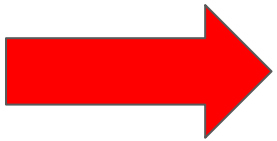
Case #2

Alfred is in for an in person apt after getting his follow-up blood work. He has had another subtherapeutic INR value. After some discussion on things that can affect INR readings, you discover that he has been eating more green leafy vegetables and exercising regularly, as him and his partner are doing a fitness and weight loss challenge. He has been enjoying this new lifestyle and expects these trends to continue.

Q1) Would you adjust the dose?

Q2) What dose would you pick?

Q3) When would you recheck INR?



Common Causes of LOW INRs	Management Strategies
MISSED DOSES, NON-COMPLIANCE, or errors in dosing	Review the doses of warfarin actually taken over the past several weeks. If patient is receiving more than one strength of tablet, consider adjusting dose to enable use of a single strength to avoid confusion. Use strategies to improve compliance: pill box, warfarin pill box or pharmacy-prepared blister packs, warfarin dosing calendar, patient education, reminder alarm, simplify dosing regimen
UNDERDOSING	Be aware that underdosing provides less protection against thrombosis but is still associated with bleeding. Bleeding risk is the similar with INRs 1.5-2.0 and 2.0-3.0, but risk of thrombosis rises quickly below INR 2.0. Aim for an INR of 2.5. Aiming for 2.0 will lead to a higher chance of underdosing. Increase the dose according to INR value.
CHANGE IN DIET/EXERCISE Increased Vitamin K-rich foods (green leafy vegetables, soy, avocado, seaweed) Meal replacement beverages containing vitamin K Increased exercise	Day-to-day and week-to-week variation in dietary vitamin K intake commonly results in variability in INR. Do not advise patients to eat less vitamin K-rich foods. Educate patient to maintain a **consistent**, healthy diet and lifestyle. If INR is low and changes are long-term, increase the warfarin dose.
DRUG INTERACTIONS	
Prescription: examples include phenytoin, carbamazepine, barbiturates, rifampin, azathioprine, trazodone	A change in INR is seen within 2 weeks of drug initiation. Increase maintenance dose of warfarin incrementally until stable maintenance dose is established.
Non-prescription: examples include green tea, ginseng, St. John's Wort	Educate patient to maintain consistency. Avoid herbal supplements, extremes of "binging" and avoidance.

FREQUENCY OF INR MONITORING

- **Initiating warfarin**: see 3 options/examples to the left; in general, week 1: Baseline, Day 3 & 5, week 2: 2 INRs, then weekly INRs until stable x 2 weeks, then q2weeks until stable x 1 month, then monthly INRs. If stable x 3 months → INR up to q12 weeks,[CHEST'12] ensure patient will report any changes in drug therapy between INRs.
- **Warfarin dose changes**: check INR weekly until stable.
- **Starting, stopping or changing the dose of an interacting drug**: check INR in 4-6 days after the change. ↑ Monitoring duration for drugs with long t½ or onset e.g. amiodarone.

MANAGEMENT OF SUB-/SUPRATHERAPEUTIC INRS see Figure & Table 3

- Interpretation of INR requires many considerations:
  - trend & time since last INR, duration of current dose full therapeutic effect may take 5-7 days
  - changes in medications (starting, stopping & changes in doses) of interacting medications, see Managing Warfarin Drug Interactions on the next page
  - factors that may ↑ INR: acute illnesses e.g. diarrhea, fever, ↑ in alcohol intake
  - factors that may ↓ INR: edema, ↑ vitamin K intake (e.g. garden harvest), ↑ physical activity level
  - patients with heart failure, diabetes & acute GI illness may experience INR instability.[8]

FIGURE: STEPWISE APPROACH FOR SUB-/SUPRATHERAPEUTIC INRs

Step 1: Note indication for warfarin & target INR. **Is the patient symptomatic for the INR?**

- If INR high, are there signs/symptoms of bleeding? Consider risk (platelet count, bleeding disorders)!
- If INR is low, are there signs &/or symptoms of a stroke or VTE?

If **yes**, provide appropriate emergent/urgent care. If **no**, proceed to Step 2.

Step 2: Is the patient <u>at risk of</u> becoming symptomatic for the INR?

- If the INR >10: hold warfarin, & give vitamin K 2.5-5mg ampule po x1.
  {ACC'20: major bleed: Vit K 5-10mg IV & consider 4F-PCC; non-major bleed: Vit K 2-5mg po/IV}
  ↓ weekly warfarin dose by 20% & resume once INR in therapeutic range. Re-check INR in ~2 days. Next day INR will likely still be elevated. Avoid IM vitamin K.
- If the INR is low, consider bridging with LMWH if the patient is at high risk of a clot.

Step 3: **Identify if sub-/supratherapeutic INR is a result of a permanent or transient cause.**

- **Transient causes**: e.g. missed/extra dose, gastroenteritis, course of antibiotics, recent ↑ alcohol intake
  - Consider dose correction e.g. hold or give extra dose & ↑ INR monitoring frequency
- **Permanent causes**: e.g. lifestyle change, change with a chronic medication
  - Consider a change in weekly dose see Table 3 below & ↑ INR monitoring frequency

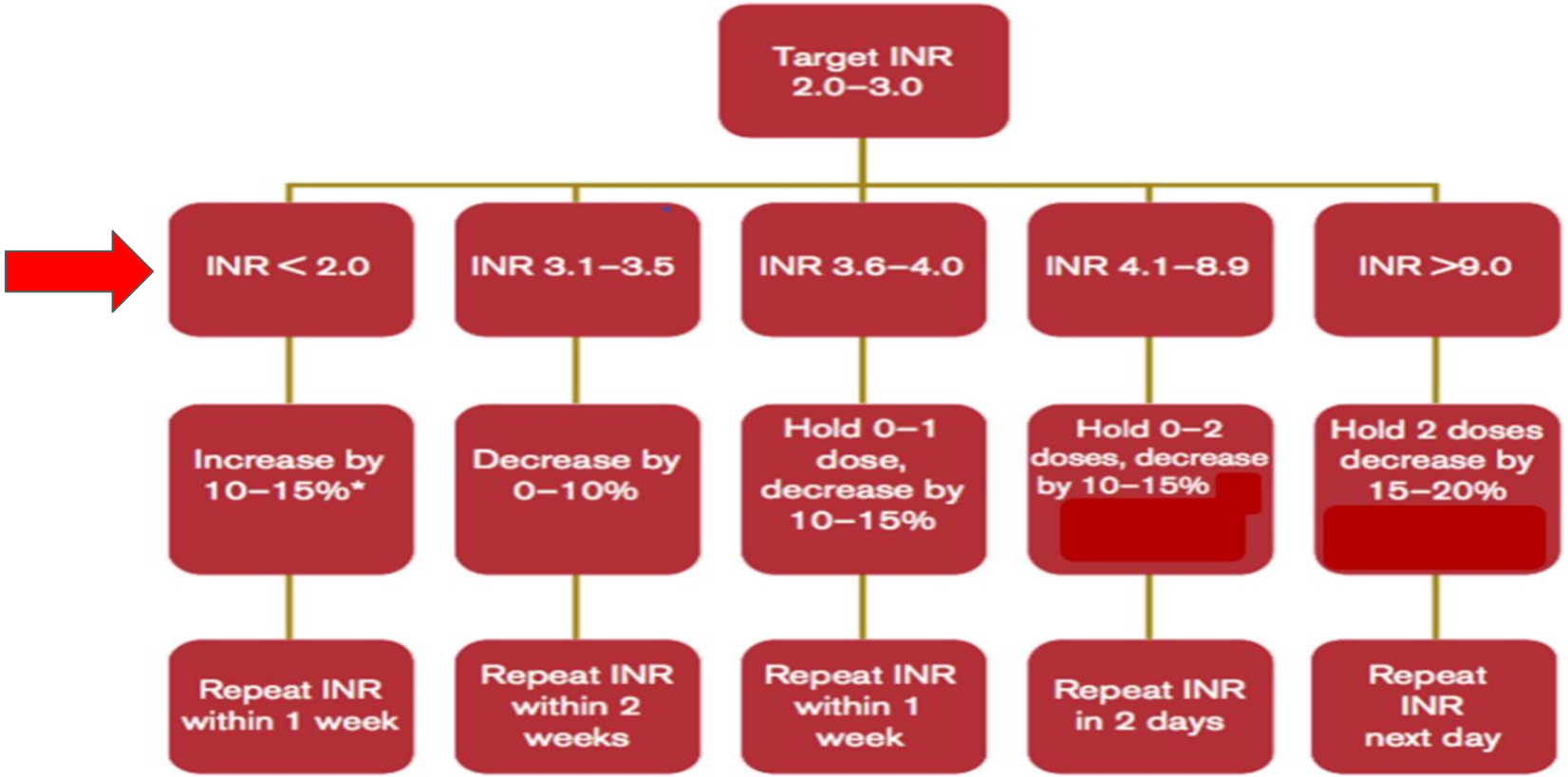
- Vitamin K 100-200 mcg po daily may help stabilize INR in pts with unexplained fluctuating INRs, but lacks evidence for routine use. Tablets are available at health food stores (e.g. GNC).
- High vitamin K doses can cause warfarin resistance for ~1 week.

TABLE 3: MAINTENANCE OF WARFARIN – EXAMPLE VALIDATED NOMOGRAM [9]

TARGET INR 2 – 3	ACTION	TARGET INR 2.5-3.5
< 1.5	Extra dose, ↑ weekly dose by 10-20%	< 2
1.5 – 1.9	↑ weekly dose by 5-10%	2 – 2.4
2 – 3	No Change	2.5 – 3.5
3.1 – 3.5	↓ weekly dose by 5-10%	3.6 – 4
3.6 – 4.9	Hold 1 dose, ↓ weekly dose by 10-20%	4.1 – 4.9
5 – 9	Hold 2 doses, ↓ weekly dose by 10-20%	5 – 9
> 9	Urgent evaluation	> 9

Do not adjust warfarin dose based on **1 asymptomatic, unexplained,** out-of-range maintenance INR **≤0.5 ± target range.** Recheck INR in 1-2 **wks.**

Figure: Warfarin Dose Adjustment in Non-bleeding Patients by % Dose Change of Total Weekly Dose (adapted from Cushman et al, 2014)



*Consider 15% increase if INR ≤1.5 without explanation

Case #2

Alfred returns. He has had another subtherapeutic INR value. After some discussion on things that can affect INR readings, you discover that he has been eating more green leafy vegetables and exercising regularly as him and his partner are doing a fitness and weight loss challenge. He has been enjoying this new lifestyle and expects these trends to continue.

Q1) Would you adjust the dose?

Yes

Q2) What dose would you pick?

4.5mg PO daily (12% ^)

Q3) When would you recheck INR?

In 1 week

Case #3

Helena is a 35-year-old female with a complicated urinary tract infection (fever, flank pain, nausea, poor oral intake). She has a history of antiphospholipid syndrome. She is currently taking warfarin 6.5mg daily and ASA 81mg daily.

Q1) Should we adjust her warfarin dose as she will be starting a long course of antibiotics?

Q2) Do we require any extra monitoring?

Lexicomp: Interactions

Title Vitamin K Antagonists / Quinolones

Print

Risk Rating C: Monitor therapy

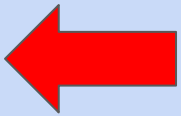
Summary Quinolones may enhance the anticoagulant effect of Vitamin K Antagonists. **Severity** Moderate **Reliability Rating** Good

Patient Management Monitor for increased INR/prothrombin time (PT) and/or toxic effects of warfarin or acenocoumarol if a quinolone antibiotic is initiated (especially during the first few days of concomitant therapy) or the dose is increased, or for decreased effects if a quinolone antibiotic is discontinued or its dose is decreased.

Quinolones Interacting Members Ciprofloxacin (Systemic), Delafloxacin, Enoxacin, Gemifloxacin, LevoFLOXacin (Oral Inhalation), LevoFLOXacin (Systemic), Levonadifloxacin, Lomefloxacin, Moxifloxacin (Systemic), Nalidixic Acid*, Norfloxacin*, Ofloxacin (Systemic), Pefloxacin, Pipemidic Acid, Prulifloxacin, Sparfloxacin, Zabofloxacin

FREQUENCY OF INR MONITORING

- **Initiating warfarin**: see 3 options/examples to the left; in general, week 1: Baseline, Day 3 & 5, week 2: 2 INRs, then weekly INRs until stable x 2 weeks, then q2weeks until stable x 1 month, then monthly INRs. If stable x 3 months → INR up to q12 weeks,[CHEST'12] ensure patient will report any changes in drug therapy between INRs.
- **Warfarin dose changes**: check INR weekly until stable.
- **Starting, stopping or changing the dose of an interacting drug**: check INR in 4-6 days after the change. ↑ Monitoring duration for drugs with long t½ or onset e.g. amiodarone.



Case #3

Helena is a 35-year-old female with a complicated urinary tract infection (fever, flank pain, nausea, poor oral intake). She has a history of antiphospholipid syndrome. She is currently taking warfarin 6.5mg daily and ASA 81mg daily.

Q1) Should we adjust her warfarin dose as she will be starting a long course of antibiotics? No

Q2) Do we require any extra monitoring? Yes. Check INR in 4-6 days

Case #3 Continued

Helena returns for warfarin management as her INR has come back at 4.2. She is not currently showing any signs of bleeding.

How can we manage warfarin dosing/monitoring?

TREATMENT OF SUPRATHERAPEUTIC INR WITHOUT BLEEDING - UpToDate

INR <4.5 without bleeding — If the INR is above the therapeutic range but <4.5 and no clinically significant bleeding is apparent, the next dose of warfarin should be omitted and/or the maintenance dose of warfarin reduced slightly (table 1) [31,37]. Often, the maintenance dose does not need to be reduced at all, especially if the INR elevation is minimal and/or expected to be transient [55]. Additional therapies such as vitamin K are not indicated in this setting. Increased monitoring (eg, INR testing once or twice a week) during the period of dose adjustment is appropriate.

Case #3 Continued

Helena returns for warfarin management as her INR has come back at 4.2. She is not currently showing any signs of bleeding.

What should we do?

Hold 1-2 doses, restart warfarin and repeat INR in 1 week, have patient self monitor for signs of bleeding.

Case #4

Q1) Does patient require interruption of warfarin?

Q2) Does this patient require bridging?

Q3) What will the INR monitoring schedule look like?

John, a 54-year-old male with a history of AF, dyslipidemia, HTN and DM2 with require surgery to remove his gallbladder (laparoscopic). He has no history of bleeding. He currently takes warfarin 6mg per day and has been stable at that dose for several years. His surgery date is set for Friday, June 30. His INR is currently 2.3.

Deciding if warfarin interruption is needed is based on the bleeding risk of the surgery/procedure (see Table 1).

Most surgeries/procedures require warfarin interruption but, in general, minimal bleed-risk procedures (e.g. dental, cataract surgery, minor skin procedures) do not need warfarin interruption.

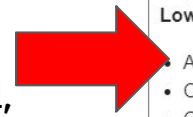


Table 1. Patient Stratification for Bleeding Risk

High-bleed-risk

- Any surgery or procedure with neuraxial (spinal or epidural) anesthesia
- Neurosurgery (intracranial or spinal)
- Cardiac surgery (e.g. CABG, heart valve replacement)
- Major vascular surgery (e.g. aortic aneurysm repair, aortofemoral bypass)
- Major orthopedic surgery (e.g. hip/knee joint replacement surgery)
- Lung resection surgery
- Urological surgery (e.g. prostatectomy, bladder tumour resection)
- Extensive cancer surgery (e.g. pancreas, liver)
- Intestinal anastomosis surgery
- Reconstructive plastic surgery
- Selected procedures involving vascular organs (e.g. kidney biopsy, prostate biopsy) or a high bleed risk intervention (e.g. pericardiocentesis, spinal injection, polypectomy)

Low/moderate-bleed-risk

- Abdominal surgery (e.g. cholecystectomy, hernia repair, colon resection)
- Other general surgery (e.g. breast)
- Other intrathoracic surgery
- Other orthopedic surgery
- Other vascular surgery
- Non-cataract ophthalmologic surgery
- Gastroscopy or colonoscopy *with* biopsies
- Coronary angiography (using femoral artery approach)
- Selected procedures with large-bore needles (e.g. bone marrow biopsy, lymph node biopsy)
- Complex dental procedure (e.g. multiple tooth extractions)

Minimal-bleed-risk

- Cataract surgery
- Dermatologic procedures (e.g. biopsy)
- Gastroscopy or colonoscopy *without biopsies*
- Coronary angiography (using radial arterial approach)
- Permanent pacemaker insertion or internal defibrillator placement (if bridging anticoagulation is not used)
- Selected procedures with small-bore needles (e.g. thoracentesis, paracentesis, arthrocentesis)
- Dental extractions (1 or 2 teeth)
- Endodontic (root canal) procedure
- Subgingival scaling or other cleaning

Is bridging anticoagulation needed during warfarin interruption?

The need for bridging is driven by patients' estimated risk for thromboembolism (see **Table 2**).

Table 2. Patient Stratification for Thromboembolism Risk

High thromboembolic risk *(bridging anticoagulation suggested)*:

- Any mechanical prosthetic mitral valve
- Older generation (cage-ball, tilting disc) mechanical aortic valve
- Chronic atrial fibrillation (valvular or non-valvular) with a $CHADS_2$ score* of 5-6
- Recent (within 3 months) arterial thromboembolism (stroke, systemic embolism, transient ischemic attack [TIA])
- Recent (within 3 months) venous thromboembolism (deep vein thrombosis, pulmonary embolism)†
- Prior arterial or venous thromboembolism during appropriate interruption of warfarin
- Severe thrombophilia with history of venous thromboembolism (e.g. deficiency of protein C, protein S or antithrombin, antiphospholipid syndrome)
- Rheumatic valvular heart disease

Intermediate thromboembolic risk *(bridging anticoagulation optional and based on individual patient characteristics)*:

- Chronic atrial fibrillation with a $CHADS_2$ score* of 3-4
- Newer generation (bileaflet) mechanical aortic valve
- Prior arterial or venous thromboembolism within last 3-12 months

Low-risk *(bridging anticoagulation is not recommended)*:

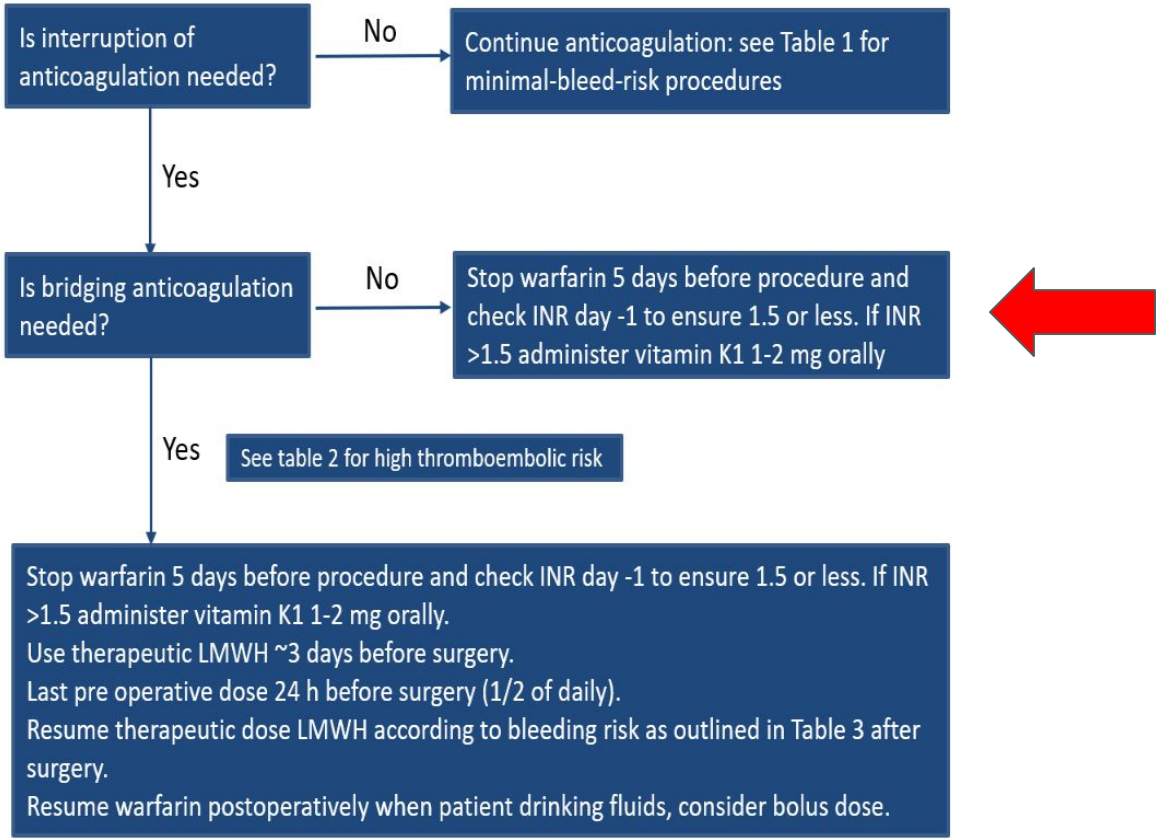
- Chronic atrial fibrillation (valvular or non-valvular) with a $CHADS_2$ score* of 0-2
- Prior venous thromboembolism over 12 months ago
- Bioprosthetic heart valve

*$CHADS_2$ score estimates the risk of stroke in patients with non-valvular atrial fibrillation. The score is the total points for the presence of congestive heart failure (1), hypertension (1), age $\geq$ 75 yrs (1), diabetes (1), stroke, transient ischemic attack or systemic embolism (2).

What is the perioperative anticoagulant management after warfarin interruption for elective procedures?

A suggested management algorithm is shown in the **Figure below.**

Figure 1. Peri-Operative Management of Warfarin-Treated Patients Before and After Surgery/Procedure



Case #4

John, a 54-year-old male with a history of AF, dyslipidemia, HTN and DM2 with require surgery to remove his gallbladder (laproscopic). He has no history of bleeding. He currently takes warfarin 6mg per day and has been stable at that dose for several years. His surgery date is set for Friday, June 30. His INR is currently 2.3.

Q1) Does patient require interruption of warfarin?

Yes

Q2) Does this patient require bridging?

No

Q3) What will the INR monitoring schedule look like?

Check INR surgery day -1, then 5-7 days after resuming warfarin

Case #5

Tanice is a 85 year old female with a history of non-valvular atrial fibrillation and end stage kidney disease. She also has a history of isolated systolic hypertension and DM2. She saw her doctor recently for warfarin adjustment 5 days ago after having 2 consecutive out of range INRs. She presented to the emergency department with melena and anemia.

Q1) How would you treat supratherapeutic INR?

Q2) What questions could you ask to investigate INR excursion?

Q3) When would you resume warfarin?

Serious/life-threatening bleeding — The following is appropriate for serious or life-threatening bleeding (table 1) [27-31]:

Discontinue warfarin

Vitamin K – Administer 10 mg vitamin K by slow intravenous infusion (eg, over 20 to 60 minutes). For most patients receiving warfarin who have severe, obvious bleeding, vitamin K can be administered without waiting for laboratory tests or imaging studies because the risks associated with vitamin K are low, and if the patient requires reinitiation of anticoagulation while refractory to warfarin, another agent such as heparin can be used. Vitamin K may be repeated at 12-hour intervals if the INR remains elevated. (See 'Vitamin K dose, route, formulation' below.)

PCC – For patients with serious bleeding and INR >2, we suggest using a 4-factor prothrombin complex concentrate (PCC, unactivated) (table 2) rather than a 3-factor PCC and/or Fresh Frozen Plasma (FFP) for rapid reversal, due to the similar efficacy and lower risk of adverse events with 4-factor PCC.

Common Causes of High INRs	Management Strategies
DRUG INTERACTIONS*	*Temporary drug interaction*: temporary warfarin hold or dose reduction. *Chronic drug interaction*: reduce maintenance dose and increase frequency of INR tests until new stable INR is achieved. **Although many drugs may interact with warfarin, avoidance of either warfarin or the interacting drug is usually not required.***
ALTERED HEALTH STATES Fever, acute illness, diarrhea, reduced food intake Uncontrolled hyperthyroidism ·CHF exacerbation	Temporarily reduce the dose and increase the frequency of INR testing until the patient's health stabilizes.
MALNUTRITION (vitamin K deficiency)	Encourage patient to consume regular meals, including those containing vitamin K. Consider meal replacement beverage. Reduce maintenance dose of warfarin and increase frequency of monitoring
ALCOHOL	A one-time moderate to large amount of alcohol (more than 2 drinks) will transiently increase the INR (e.g., weekend party). Continue usual maintenance dose.
NON-COMPLIANCE OR ERRORS IN DOSING (The patient mistakenly took a different dosage regimen than was prescribed)	Review the doses of warfarin actually taken over the past several weeks. Use strategies to improve compliance: pill box, warfarin dosing calendar, patient education, simplify dosing regimen.

***Most common drugs that can increase INR:**

- Antibiotics: sulfamethoxazole/trimethoprim, metronidazole, quinolones (ciprofloxacin, levofloxacin), amoxicillin, erythromycin, clarithromycin, azithromycin
- Azole antifungals: fluconazole, voriconazole
- Cardiac drugs: amiodarone, some statins (atorvastatin and pravastatin are least likely to interact), fenofibrate
- Acetaminophen >1 g/day
- Levothyroxine dose changes– full effect observed after 4-6 weeks of dose change

WARFARIN DOSING

- For confirmed or suspected **DVT or PE**, start warfarin on day 1 (see options under "Initiating Warfarin" above).
  - When cross-covering with parenteral anticoagulant e.g. heparin or **LMWH**,[10] even if INR >2, a minimum 5 days of overlap is required [10,11] regardless of initial dosing; i.e. warfarin + LMWH x 5 days & until INR > 2.
  - When initiating warfarin, INR may be elevated before fully anticoagulated ? hypercoagulable due to protein C deficiency, t½ = 6hours.
  - With these 2 things in mind: **the higher the dose the higher the potential to overshoot the INR, possibly prompting early discontinuation of LMWH before true anticoagulation effect of warfarin has taken effect.**
- The **average warfarin dose** is 4-6 mg daily (daily range ≤0.5 – ≥25 mg), & has an inverse relationship with age (e.g. 6.3 mg daily in 50 yrs, 3.6 mg daily in 70 yrs) [12]
- **Is there an upper limit for warfarin doses?** Probably *not*, however, if ↑dose & otherwise inexplicable, investigate absorption or nonadherence → deliberate or inadvertent e.g. verify dose using colours of tablets.
  - warfarin tablet strengths & colours:

- Most **dose changes will be < 15% of weekly warfarin dose** see Table 3. To calculate weekly warfarin dose:
  1) Simply add last 7 days make note of any vitamin K that might have been given & will blur interpretation of the weekly dose
  2) Multiply the weekly total by the percent change based on Table 3 on previous page
  3) Add or subtract the weekly dose change to different days of the week
  - Example: INR today 1.8 (target 2-3) maintenance, ↑ activity level with new workout program
    1) Last 7 days doses: 6 mg, 6 mg, 6 mg, 6 mg, 6 mg, 6 mg, 6 mg → 6 mg/day x 7 days/week = 42 mg/week
    2) 42mg/week x 5% = 2 mg (5% based on Table 3)
    3) Add 2 mg per week → consider adding 1 mg extra to Mondays & Fridays; i.e. 7 mg on Mondays & Friday, 6 mg all the other days of the week.
- Dosing calculator: www.warfarindosing.org

Note: **Acenocoumarol SINTROM** (1mg, 4mg; $30-$74) considered an alternative to warfarin for those patients with warfarin intolerances, other than bleeding.

WARFARIN MONITORING

- Less experienced clinicians may benefit more from using a nomogram, BUT even most high-capacity anticoagulation clinics e.g. 100s of patients use a nomogram.
- Anticoagulation Clinics may improve TTR absolute ↑ ~8%.
- Patient self-monitoring/self-testing has some supporting evidence ↓clots & bleeds but is reserved for special cases +++motivation /training/education; ensure device regulated by Health Canada: Medical Devices Active Licenses Search www.hc-sc.gc.ca/dhp-mps/md-im/licen/mdlic-eng.php
  (**NIHB coverage** ✓ for INR monitors & supplies)
- Pharmacogenetic testing likely helps predict dose, but is not associated with improvement in important clinical outcomes such as bleeding or thrombotic events (may reach therapeutic INR sooner);[13] currently not available in SK and not supported by the guidelines. CHEST'12; GIFT, EU-PACT,COAG

MANAGING WARFARIN DRUG INTERACTIONS

- Avoid interacting drugs when possible [CHEST'12] e.g. verify indications, select non-/less interacting alternatives.
- Assume there is an interaction with any drug start, stop, or dose change. May need to check ≥2 references; many inclusion/omission conflicts across major references.
  - Review of 4 references: 3 common compendia & the warfarin's product monograph. Collectively, 648 total drug & food interactions→ only 50 common to all 4 references.[14]
- Warfarin interactions can be divided into 2 categories:
  1) Interactions that cause a change in INR: e.g. **amiodarone** delayed x days/weeks/months, **antiepileptics**, **antimicrobials** especially cotrimoxazole, ciprofloxacin, clarithromycin, metronidazole, **corticosteroids**. If combination cannot be avoided, ↑ INR monitoring & reactively adjust dose in response. Empiric dosage adjustments rarely necessary & are less predictable than the interaction itself.
  2) Interactions that ↑risk of bleed or clot without affecting INR: e.g. **NSAIDs, antiplatelets, hormone therapy**. These interactions require a balance of the risk (bleeding, clotting) with the benefit of therapy.
- Most/any **antibiotic** can interact with warfarin by disrupting normal GI flora, thereby disrupting vitamin K conversion/cycle.
- Very few, if any, combinations are absolutely contraindicated.
- **Thyroid** medications can cause counter-intuitive for some reactions:
  - Levothyroxine ↑ INR ↑ catabolism of clotting factors
  - Methimazole & propylthiouracil ↓ INR
- Many serious & unpredictable **herbal** interactions
  see RxFiles Herbal Drug Interactions Chart pgs 221-222

MANAGING WARFARIN FOOD INTERACTIONS

- Encourage **consistent** vitamin K intake.
- Empiric dose changes for altered vitamin K intake (e.g. garden season) are unpredictable, therefore monitor INR more frequently & adjust dose as required; exception: ↑ INR monitoring not necessary when previous fluctuations in vitamin K intake had little impact on INR.

ANTICOAGULATION BRIDGING [TC'20] see pages 11 & 12

- Anticoagulation bridging during warfarin interruption can be considered for patients at intermediate to high risk of thrombosis. See Perioperative chart pg 11.
- Due to the lack of high-quality evidence, the decision to bridge should be tailored to the patient & balance the risk of clotting & bleeding both the patient's baseline risk & risk associated with the procedure:
  - **Low risk of thrombosis** e.g. $CHADS_2$ score 0-2 without hx of stroke/TIA, VTE >12 months ago with no other risk factors, bioprosthetic heart valve **& non-/minimally-invasive procedures**: continue warfarin.
    - **Minor dental** procedures: continue warfarin & consider topical prohemostatic agents, e.g. tranexamic acid 5mL (100mg/mL) po 5-10 minutes pre-procedure, & 3-4x/day for 1-2 days post-procedure.[CHEST'12]
  - **Intermediate risk of thrombosis** e.g. $CHADS_2$ score 3-4, VTE 3-12 months ago, newer mechanical aortic valve: balance risk of bleeding & clotting.
  - **High risk of thrombosis** e.g. $CHADS_2$ score 5-6, VTE or stroke/TIA ≤3 months ago, prior thromboembolism with warfarin interruption, mechanical mitral valve, older mechanical aortic valve, rheumatic valvular heart disease, severe thrombophilia with history of VTE: consider anticoagulant bridging (e.g. LMWH).

RESTARTING WARFARIN POST-INTRACEREBRAL BLEED

- Retrospective cohort study 19 tertiary centres in Germany, 2006 to '12.[18] Warfarin restarted in 172/719 (23.9%), AF n=566. Mean $CHADS_2$ 2.5 & HASBLED 3.1, median INR 2.8 (IQR 2.3-3.5). Those who restarted warfarin had ↓ ischemic complications (5.2% [9/172] versus not on warfarin 15% [82/547], p<0.001), but bleeding & recurrent intracerebral hemorrhage non-statistically significant. Median time for warfarin resumption was 31 days (IQR 18-65). Consider restarting warfarin after 4-8 weeks.[ESC'18]

AF=atrial fibrillation **ASA**=acetylsalicylic acid **DI**=drug interactions **DVT**=deep vein thrombosis **HF**=heart failure **hx**=history **GI**=gastrointestinal **INR**=international normalized ratio **LMWH**=low molecular weight heparin **NSAID**=non-steroidal anti-inflammatory drugs **PE**=pulmonary embolism TIA=transient ischemic attack **SK**=Saskatchewan **t½**=half-life **TTR**=time in therapeutic range **VTE**=venous thromboembolism **yr**=years old

Management of warfarin-associated bleeding or supratherapeutic INR - UpToDate

Gastrointestinal bleeding — For a patient receiving warfarin who has gastrointestinal bleeding, endoscopy can be both diagnostic and therapeutic. Bleeding should not be attributed solely to anticoagulation, and the source of bleeding should be pursued as done for patients not receiving an anticoagulant. Details of the evaluation are presented separately according to the age of the patient and the acuity of bleeding:

Patients on warfarin **-** We restart warfarin in the evening of the procedure day, if no further bleeding occurs. Patients who resume warfarin will require several days to achieve therapeutic levels of anticoagulation.

For those patients who had high enough thrombotic risk to warrant bridge therapy, we restart intravenous unfractionated heparin 48 hours after hemostasis is achieved for patients who require bridge therapy

Case #5

Tanice is a 85 year old female with a history of non-valvular atrial fibrillation and end stage kidney disease. She also has a history of isolated systolic hypertension and DM2. She saw her doctor recently for warfarin adjustment 5 days ago after having 2 consecutive out of range INRs. She presented to the emergency department with melena and anemia.

Q1) How would you treat supratherapeutic INR?

Vitamin K 10mg IV by slow infusion. 4 factor PCC

Q2) What questions could you ask to investigate INR excursion?

Dosing errors? Medication interactions? Changes in diet/exercise/health

Q3) When would you resume warfarin?

After endoscopy, if hemostasis has been achieved.

MANAGEMENT PEARLS

- Use a validated nomogram for initiating & maintaining warfarin. Nomograms have been shown to ↑ time in therapeutic range (TTR) see Tables 1, 2 & 3.[CADTH, CHEST '16, 3]
- Extend the frequency of international normalized ratio (INR) monitoring to q12wks in pts who have had stable INRs for ≥3 mos,[CHEST'16] ensure pt will report any drug changes between INRs.
- In pts maintained on warfarin, do not adjust dose based on an asymptomatic, single, unexplained e.g. no drug/dietary Δ, out-of-range INR **≤0.5 ± target range**; recheck in 1-2 wks.[2,4]
- If concomitant use of a drug that alters INR cannot be avoided, ↑ INR monitoring & reactively (**not** proactively) adjust the dose in response, except if can predict response based on past DI.

Thanks!

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