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 '12, 3]
- Extend the frequency of international normalized ratio (INR) monitoring to q12wks in pts who have had stable INRs for ≥3 mos,[CHEST'12] 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

- 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]

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

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

- 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).

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

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

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'17: Vit K 5-10mg IV if major/life threatening bleed; ? Vit K 2-5mg po/IV if non-major bleed}
  ↓ 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.**

WARFARIN TIPS & DOSING NOMOGRAMS

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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 ? hypercoaguable 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 ↑ & otherwise inexplicable, investigate absorption or non-compliance → deliberate or inadvertent e.g. verify dose using colours of tablets.
  - generic Taro-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-$70) 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
- 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, 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.

MANAGING WARFARIN DRUG INTERACTIONS continued

- **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 pg 137: http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-herbal-di.pdf

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 also see pages 15 & 16

- Anticoagulation bridging during warfarin interruption can be considered for patients at moderate to high risk of thrombosis.[CHEST'12] See Perioperative chart pg 16.
- Due to the lack of high-quality evidence,[CHEST'12 ,15] 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 **& non-/minimally-invasive procedures**: continue warfarin.
    - **Minor dental** procedures: continue warfarin with 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]
  - **Moderate risk of thrombosis** e.g. $CHADS_2$ score 3-4, VTE 3-12 months ago: balance risk of bleeding & clotting. [CHEST'12]
  - **High risk of thrombosis** e.g. $CHADS_2$ score 5-6, VTE or stroke/TIA ≤3 months ago, mechanical valve (especially mitral): consider anticoagulant bridging (e.g. LMWH).[CHEST'12]

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**=acetylsalicyclic 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

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REFERENCES FOR WARFARIN TIPS & DOSING NOMOGRAMS

1) Canadian Agency for Drugs and Technologies in Health. Optimal warfarin management for the prevention of thromboembolic events in patients with atrial fibrillation: a systematic review of the clinical evidence [Internet]. Ottawa: The Agency; 2011 Nov [cited 2011 Nov 21]. (Optimal use report; vol. 1 iss. 2a). Available from: http://www.cadth.ca/media/pdf/OP0508_warfarin-science-report-1_clinical_e.pdf.
2) Holbrook A, Schulman S, Witt D, Vandvik P, et al.,. Evidence Based Management of Anticoagulant Therapy: Antithrombotic Therapy and Prevention of Thrombosis, American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (9th Edition). Chest. 2012; 141:152s-184s.
3) Kim YK, Nieulaat R, Connolly SJ, et al. Effect of a simple two-step warfarin dosing algorithm on anticoagulant control as measured by time in therapeutic range: a pilot study. Journal of Thrombosis and Haemostasis. October 2009. 8: 101-106.
4) Ageno W, Gallus AS, Wittkowsky A, et al.,. Oral Anticoagulant Therapy**,** American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (9th Edition). Chest. 2012; 141:44s-88s.
5) Harrison L, Johnston M, Massicotte MP, et al. Comparison of 5-mg and 10-mg Loading Doses in Initiation of Warfarin Therapy. Ann Intern Med. 1997;126:133-136.
6) Crowther MA, Harrison L, Hirsh J. Warfarin: less may be better [Letter]. Ann Intern Med. 1997;127:333.
7) Kovacs MJ, Rodger M, Anderson DR, et al. Comparison of 10-mg and 5-mg Warfarin Initiation Nomograms Together with Low-Molecular-Weight Heparin for Outpatient Treatment of Acute Venous Thromboembolism. Ann Intern Med. 2003;138:714-719.
8) Ageno W, Gallus A, Wittkowsky A, Crowther M, et al. Oral Anticoagulant Therapy: Antithrombotic Therapy and Prevention of Thrombosis American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (9th Edition). Chest. 2012; 141:44s-88s.
9) University of Wisconsin Anticoagulation Services: Ambulatory Warfarin Management; Warfarin Dosing Algorithm. May 31, 2012. www.uwhealth.org.
10) Levine M, Gent M, Hirsh J, Leclerc J, Anderson D, Weitz J, et al. A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. N Engl J Med. 1996;334:677-81. [PMID: 8594425]
11) Low-molecular-weight heparin in the treatment of patients with venous thromboembolism. The Columbus Investigators. N Engl J Med. 1997;337:657- 62. [PMID: 9280815]
12) Horton JD, Bushwick BM. Warfarin Therapy: Evolving Strategies in Anticoagulation. Am Fam Physician. 1999 Feb 1;59(3):635-646.
13) Le Gal G, Carrier M, Tierney S, et al. Prediction of the warfarin maintenance dose after completion of the 10 mg initiation nomogram: do we really need genotyping? Journal of Thrombosis & Haemostasis. Jan 2010;8(1):90-4.
14) Anthony M, Romero K, Malone DC, et al. Warfarin interactions with substances listed in drug information compendia and in the FDA-approved label for warfarin sodium. Clin Pharmacol Ther. 2009;86(4): 425-429.
15) Siegal D, Yudin J, Kaatz S, et al. Periprocedural heparin bridging in patients receiving vitamin K antagonists: systematic review and meta-analysis of bleeding and thromboembolic rates. Circulation 2012:126(13):1630-1639.
16) Douketis JD, Spyropoulos AC, Spencer FA, et al. Perioperative Management of Antithrombotic Therapy Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012; 141:326s-350s.
17) Garcia P, Ruiz W, Loza Munarriz C. Warfarin initiation nomograms for venous thromboembolism. Cochrane Database Syst Rev. 2013 Jul 10;7:CD007699. In patients with acute thromboembolism (DVT or PE) aged 18 years or older, considerable uncertainty surrounds the use of a 10-mg or a 5-mg loading dose for initiation of warfarin to achieve an INR of 2.0 to 3.0 on the fifth day of therapy. Heterogeneity among analyzed studies limits certainty surrounding optimal warfarin initiation nomograms.
18) Kuramatsu JB, Gerner ST, Schellinger PD, et al. Anticoagulant reversal, blood pressure levels, and anticoagulant resumption in patients with anticoagulation-related intracerebral hemorrhage. JAMA. 2015 Feb 24; 313(8):824-36.
19) Boonyawat K, Wang L, Lazo-Langner A, et al. The effect of low-dose oral vitamin K supplementation on INR stability in patients receiving warfarin. A randomised trial. Thromb Haemost.2016 Aug 30;116(3):480-5.
20) Gage BF, Bass AR, Lin H, et al. Effect of **genotype-guided warfarin dosing** on clinical events and anticoagulation control among patients undergoing hip or knee arthroplasty: the **GIFT** randomized clinical trial. JAMA. doi:10.1001/jama.2017.11469
21) Verhoef TI, Ragia G, de Boer A, et al. A randomized trial of **genotype-guided dosing of acenocoumarol and phenprocoumon**. (**EU-PACT**) N Engl J Med 2013. DOI: 10.1056/NEJMoa1311388.
22) Pirmohamed M, Burnside G, Eriksson N, et al. A randomized trial of **genotype-guided dosing of warfarin**. (**EU-PACT**) N Engl J Med 2013. DOI: 10.1056/NEJMoa1311386.
23) Kimmel SE, French B, Kasner SE, et al. A **pharmacogenetic versus a clinical algorithm for warfarin** dosing. (**COAG**) N Engl J Med 2013. DOI: 10.1056/NEJMoa1310669
24) Stergiopoulos K, Brown DL. **Genotype-guided vs clinical dosing** of warfarin and its analogues: meta-analysis of randomized clinical trials [online June 16, 2014]. JAMA Intern Med. doi:10.1001/jamainternmed.2014.2368.
25) Writing Committee, Tomaselli GF, Mahaffey KW, et al. **2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants**: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol. 2017 Nov 10.
26) Behera SK, Xavier AS, Selvarajan S, et al. **Acenocoumarol** As An Alternative Anticoagulant In A Patient With Warfarin Related Nephropathy. Br J Clin Pharmacol. 2018 Feb 8.
27) Biffi A, et al. Oral Anticoagulation and Functional Outcome after Intracerebral Hemorrhage. Ann Neurol. 2017 Nov;82(5):755-765. doi: 10.1002/ana.25079.
28) Steffel J, et al; ESC Scientific Document Group . The **2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation**. Eur Heart J. 2018 Apr 21;39(16):1330-1393.