وزارة الصحة
Ministry of Health

Clinical Practical Guidance for Warfarin Monitoring for Adult

Clinical Pharmacy Department
General Administration of Pharmaceutical Care
Assistant Deputy Minister for Supporting Medical Services
Ministry of health

وزارة الصحة
Ministry of Health

	Name:	Title:	Administration Department:
Prepared by	*Rasha M. Al-Zahrani*	*Clinical Pharmacist, TQM Dip.*	*General administration of pharmaceutical care*
Reviewed by	*Mohammad A. Al-shennawi*	*Pharmacist, Pharm., M.B.A*	*General director, General administration of pharmaceutical care*
	Alaa S. Mutlaq	*Senior Clinical Pharmacist in Internal Medicine*	*General administration of pharmaceutical care*
	Abdulmajeed Shoieb Alharbi	*Senior Clinical Pharmacist*	*KFSH, Qassim*
	Esraa Khalid Badawi	*Senior Clinical Pharmacist*	*KFH, Jeddah*
	Fawaz Hamdan Alharbi	*Senior Clinical Pharmacist*	*KSH, Unaizah*
	Hussain Ahmed Alhaider	*Clinical Pharmacist*	*KKH, Najran*
	Lujin Abdu Khayyat	*Clinical Pharmacist*	*KFH, Jeddah*
	Maram Abu Zaid	*Senior Clinical Pharmacist*	*PMAH, Riyadh*
	Samah S. Basudan	*Senior Clinical Pharmacist*	*KFH, Jeddah*
	Taibah A. AbuTaki	*Senior Clinical Pharmacist*	*DESH, Eastern Region*
	Elham F. Sabbage	*Pharmacist*	*General administration of pharmaceutical care*
	Saleh F. Alqifari	*Consultant Clinical Pharmacist in Ambulatory Care*	*Buraydah Private Colleges, Buraydah, Qassim*

وزارة الصحة
Ministry of Health

A-Introduction:

- Anticoagulant medicines reduce the ability of the blood to clot (coagulation means clotting). This is necessary if the blood clots too much, as blood clots can block blood vessels and lead to conditions such as a stroke or a heart attack.
- The two most common anticoagulant medicines are heparin, and warfarin.
- This guidance is established by General Administration of pharmaceutical care, Ministry of Health for anticoagulation clinics.
- Anticoagulation clinic is a collaborative service between the clinical pharmacist and physician to provide proper use of warfarin.

I. Proposes:

- This guidance has been developed to guide the clinical pharmacist who run the anticoagulation clinic for monitoring the warfarin dose, optimizing the patient education, and reducing of adverse events in all patients treated with warfarin.

II. Aims and scope:

- Activating the role of the clinical pharmacist in anticoagulation clinics, including reducing the load on the treating physician and reducing patient waiting time.
- Adjusting and determining the appropriate dosage for warfarin in adult patients.
- Determining the laboratory tests necessary for pharmacological monitoring in adult patients.
- Defining the time intervals for regular anticoagulation controls.
- Assessing the potential pharmacological interactions in adult patients.
- Carrying out educational programs for adult patients and healthcare providers.

III. Targeted population:

- Adult patients using warfarin with the specific criteria (determine by physician and clinical pharmacist in agreement form and policy).

IV. Targeted end users:

- Clinical pharmacists.

V. Setup:

- Ambulatory Care Diabetes Clinics.

VI. Methodology:

- Development of anticoagulation Pharmacotherapy Clinic Guideline completed by reviewing and adopting the international guidelines and pharmacotherapy references, literature review, and the MOH formulary. Then the panel of experts in the field of clinical pharmacists reviewed it. Finally, the guideline reviewed and amended by consultant clinical pharmacists in care internal medicine and ambulatory care clinics.

- We agree on these reviews with more than 75% of the members' votes, In the event of a disagreement, the reviews should be worked on again until an agreement is reached that exceeds this percentage.
- Team members reviewed this guidance in several sessions for editing, updating, improving, reviewing, taking expert opinions, and annual updating if any changes or updates released by international/national guidelines.
- policies-procedures and an agreement form should be developed by hospital according to hospital quality standers.

VII. Conflict of interest:

- This guidance developed based on valid scientific evidence, critical assessment of that evidence, and objective clinical judgment that relates the evidence to the needs of practitioners and patients. No financial relationships with pharmaceutical, medical device, and biotechnology companies.

VIII. Funding:

- No fund was provided.

IX. Updating:

- First version of this guidance created in 2020. The guidance will be updated annually if any changes or updates released by international/national guidelines, pharmacotherapy references or MOH formulary.

X. Evidence-grading system

Level of evidence/recommendations	Description
Grade 1	Recommendations are strong recommendations that can be applied to most patients
Grade 2	Recommendations are weaker recommendations.
Grade a	Recommendations are supported by high-quality evidence
Grade b	Recommendations are based on randomized clinical trials With methodological flaws or inconsistent results
Grade c	Recommendations are based on weaker evidence
Grade e	Expert consensus or clinical experience

B- General Guidance:

1- Patients taking warfarin should be treated using systematic processes of care to optimize effectiveness and minimize adverse effects. Health care professionals skilled in the initiation and assessment of therapy and dosing adjustments can dramatically influence outcomes (grade B).[8]
2- The initiation of warfarin therapy usually starts by main responsible physician at hospital setting.
3- All patients on warfarin should refer to anticoagulation clinic according to the arranged appointment.
4- The clinical pharmacist should evaluate the patient criteria for considering the direct oral anticoagulants (DOACs) if possible and discussing it with the responsible physician.
5- If DOACs are not indicated or DOACs are contraindicated, the patient will be eligible for follow up in warfarin clinic.
6- In patients with atrial fibrillation and at least one other risk factor for stroke, newer agents (rivaroxaban and dabigatran that do not require frequent laboratory monitoring are as effective as warfarin for prevention of stroke or systemic embolism and have comparable risks of major bleeding(grade A)[8].
7- Each patient should have a card/ booklet for follow up when arriving to the clinic filled by main responsible physician and information should include (but not limited to):
    a. Patient's Information (name, age, gender, allergy, diagnosis, duration…etc.)
    b. Target international normalized ratio (INR) level (determined by main treating physician)
    c. History of bridging therapy.
    d. Summary of education material (How to take warfarin, actions taken if extra doses are taken by mistake, side effects, visiting dentist clinic instruction, drug-drug interaction, food-drug interaction, pregnancy and Breastfeeding, instruction when warfarin is stopped.
8- In each visit the clinical pharmacist will write the date, INR level (the level should be measured in the same day or at least one day before) and newly adjusted dose (table 1a,1b & chart 1).
9- The next appointment will be arranged based on INR result (table 2).

Table (1a): If the Goal 2-3:

INR	Suggested change in total "weekly "dosage.
< 1.5	Give extra daily dose once and increase weekly dose by 10%-20%[c]
1.5-1.9	Increase weekly dose by 5%-15% (may give extra daily dose ×1)[b,c]
2.0-3.0	Maintain same dose (If INR goal is achieved)
3.1-4.0[a]	Hold zero to one daily dose and decrease weekly dose by 5%-20% [b]
≥ 4.1	Refer to chart (1)

Table (1b): If the Goal 2.5-3.5:

INR	Suggested change in total "weekly "dosage.
< 1.9	Give extra daily dose once and increase weekly dose by 10%-20%[c]
1.9- 2.4	Increase weekly dose by 5%-15% (may give extra daily dose ×1)[b,c]
2.5-3.5	Maintain same dose (If INR goal is achieved)
3.6-4.0[a]	Hold zero to one daily dose and decrease weekly dose by 5%-20% [b]
≥ 4.1	Refer to chart (1)

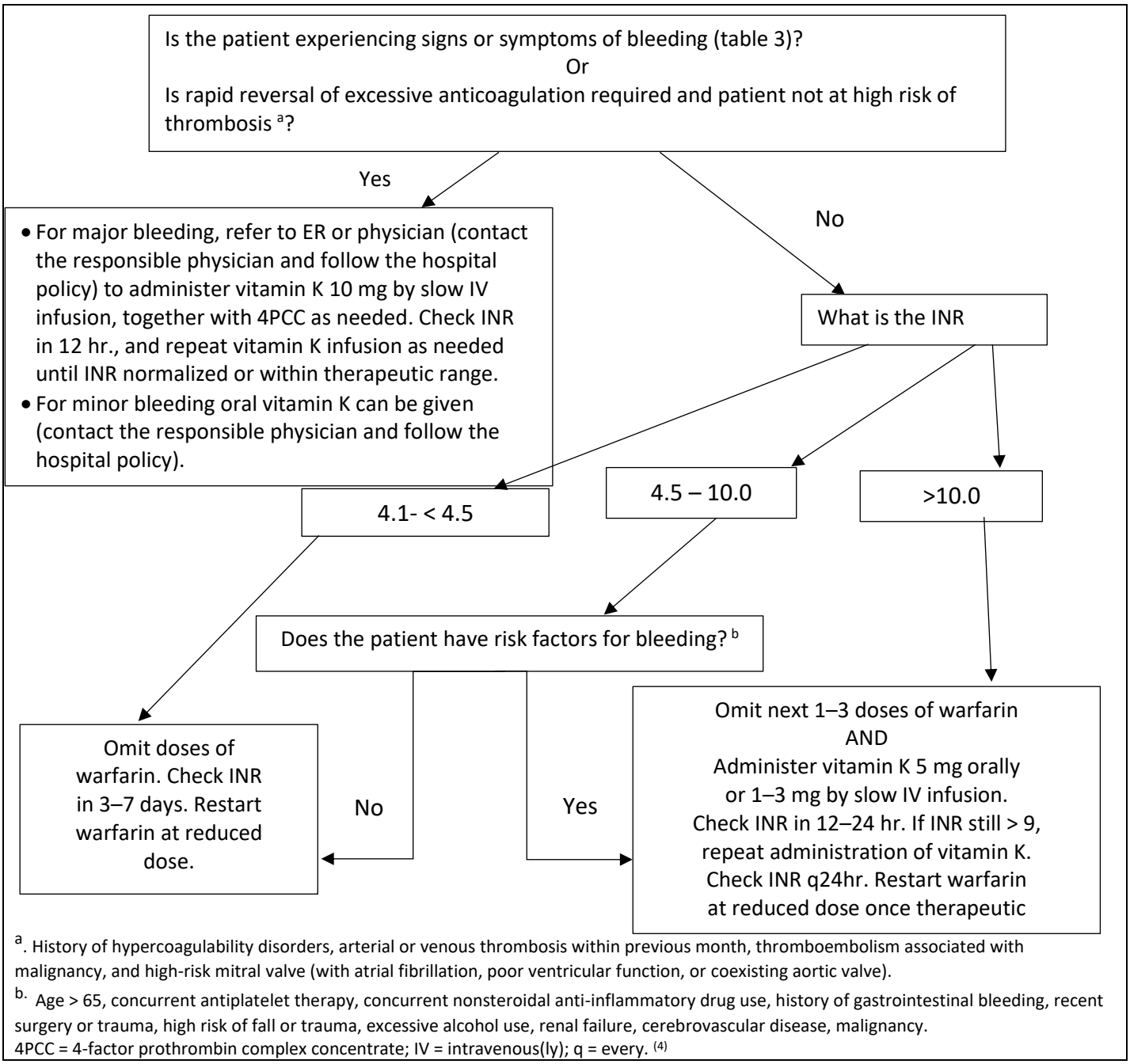
[a.] Assumes no active bleeding or minor bleeding complications
[b.] If transient cause is identified or if previously stable and INR ≤ 0.5 unit is out of range, may not need to increase/decrease weekly dose. [3]
[c.] Considers bridging therapy for 5 days with Low Molecular Weight Heparin (LMWH) if INR less than the target level especially in patient who may possibly develop thrombosis example: patient with venous thromboembolism (VTE)and atrial fibrillation (Level E).

Table (2): Frequency of Monitoring by Clinical Setting: [a] [5]

Initiation of therapy	Frequency of monitoring
After hospital discharge	- **If stable,** within 3 to 5 days until INR within therapeutic range on 2 consecutive INR checks. - **If unstable**, within 1 to 3 days until INR within therapeutic range on 2 consecutive INR checks. - Then every week until INR within therapeutic range on 2 consecutive INR checks. - Then every 2 weeks until INR within therapeutic range on 2 consecutive INR checks. - Then every 4 weeks when dose is stable check monthly.
Outpatient flexible initiation	Daily through day 4, then within 3 to 5 days.
Outpatient average daily dosing method	Every 3 to 5 days until INR reaches lower limit of therapeutic range, then within 1 week.
Maintenance therapy	**Frequency of monitoring**
Routine follow-up in medically stable [C] and reliable patients	Every 4 to 12 weeks.
Routine follow-up in medically unstable or unreliable patients	Every 1 to 2 weeks.
Dose held today for significant over-anticoagulation	Recheck in 1 to 2 days.
Dosage adjustment by 5-10% today	Recheck within 1 to 2 weeks. [b]
If dose adjusted by 10-20%, starting or stopping an interacting medication, change in diet, change in activity level or other change that could affect INR	Recheck within 1 week. [b]

[a] These example suggestions should not replace clinical judgment; more frequent monitoring may be necessary.
[b] After any dose change the INR level should be rechecked every week until INR within therapeutic range on 2 consecutive INR checks then every 2 weeks until INR within therapeutic range on 2 consecutive INR checks then every 4 weeks When dose is stable check every 4 to 12 weeks.
[c] Medically stable: INR should be monitored up to every 12 weeks in patients who are stable, which is defined as having at least three months of consistent results with no need to adjust warfarin dosing (grade 2B)[8].

Chart (1) Management of bleeding and/or elevated INRs with warfarin therapy:



[a]. History of hypercoagulability disorders, arterial or venous thrombosis within previous month, thromboembolism associated with malignancy, and high-risk mitral valve (with atrial fibrillation, poor ventricular function, or coexisting aortic valve).

[b]. Age > 65, concurrent antiplatelet therapy, concurrent nonsteroidal anti-inflammatory drug use, history of gastrointestinal bleeding, recent surgery or trauma, high risk of fall or trauma, excessive alcohol use, renal failure, cerebrovascular disease, malignancy.

4PCC = 4-factor prothrombin complex concentrate; IV = intravenous(ly); q = every. (4)

Table (3): Common Signs and Symptoms of major bleeding and clotting[6,7]

Signs and Symptoms of major bleeding	Signs and Symptoms of clotting
Blood in urine or stool (enough to color toilet water)	Chest or unilateral leg pain
Blood in sputum	Shortness of breath
Bloody emesis (bright red or coffee ground-like)	Elevated heart rate (HR > 100bpm)
Bleeding that has not resolved or slowed within 10 minutes	Unilateral lower extremity swelling

10- Key Elements of Patient Education Regarding Warfarin:

- Identification of generic and brand names.
- Purpose of therapy.
- Expected duration of therapy.
- Dosing and administration.
- General information about INR (what is the INR, why we need to monitor it …..etc)
- Target INR and expected monitoring frequency.
- Visual recognition of drug and tablet strength.
- Information concerning for missed dose.
- Recognition of signs and symptoms of bleeding/ thromboembolism.
- What to do if bleeding or thromboembolism occurs
- Drug-drug interactions and natural/herbal products
- Alcohol use
- pregnancy
- Drug-Food interactions (Dietary instructions especially with the amount of Vitamin K-rich foods)
- Information concerning surgical/dental procedures.
- Information concerning minor & major trauma.

وزارة الصحة
Ministry of Health

References:

1- MARK H. EBELL, M.D., M.S., *Athens, Georgia Am Fam Physician.* 2005 Feb 15;71(4):763-765
2- Adapted with permission from Kovacs MJ, Rodger M, Anderson DR, Morrow B, Kells G, Kovacs J, 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. A randomized, double-blind, controlled trial. Ann Intern Med 2003; 138:716.
3- ACCP Updates in Therapeutics® 2014: The Pharmacotherapy Preparatory Review and Recertification Course
4- ACCP Updates in Therapeutics® 2019: The Pharmacotherapy Preparatory Review and Recertification Course
5- Adapted from Wittkowsky 2018
6- Kearon C, Akl E, Comerota A, 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: 419s-494s.
7- Dupras D, Bluhm J, Felty C, et al (2013) Institute for clinical systems improvement: venous thromboembolism diagnosis and treatment. Available via http://bit.ly/VTE0113. Accessed March 10, 2015
8- Updated Guidelines on Outpatient Anticoagulation, (Am Fam Physician. 2013;87(8):556-566. Copyright © 2013 American Academy of Family Physicians.)

C- Warfarin: Drug information:

Brand Names in KSA: Coumadin; Coufatex

Pharmacological Category: Anticoagulant; Anticoagulant, Vitamin K Antagonist

Dosing Adult:

Dosing must be individualized and use of an institutional protocol is recommended [(1).] Response to warfarin is influenced by numerous factors (example; age, organ function). Genetic variations in metabolism (e.g. CYP2C9 and/or VKORC1 genes) can impact warfarin sensitivity; however, routine genetic testing is not recommended [(2).]

Oral:

Initial: 5 -10 mg once daily for most patients. A lower or higher starting dose may be used depending upon patient-specific factorsa."initiated in healthy outpatients with acute Thromboembolism" (grade 2C)[17] **(see example warfarin initiation table and nomogram below).** Although an elevation in INR can be seen as soon as 24 to 48 hours after the first dose due to depletion of factor VII, this does not represent therapeutic anticoagulation because other vitamin K–dependent clotting factors with longer half-lives (e.g. factors II, IX, and X) must also be depleted. Accordingly, in patients at high risk for thromboembolism, overlap ("bridging") with a parenteral anticoagulant may be necessary during initiation (or monitoring) of warfarin until a stable therapeutic INR is attained. [(3)]

a. 5-mg warfarin (Coumadin) Therapy:

Table (1): 5 mg initial daily warfarin therapy approach [(1)]

Day	INR	DOSE (MG)
1	—	5.0
2	—	5.0
3	< 1.5	10.0
	1.5 to 1.9	5.0
	2.0 to 3.0	2.5
	> 3.0	0.0
4	< 1.5	10.0
	1.5 to 1.9	7.5
	2.0 to 3.0	5.0
	> 3.0	0.0
5	< 2.0	10.0
	2.5 to 3.0	5.0
	> 3.0	0.0
6	< 1.5	12.5
	1.5 to 1.9	10.0
	2.0 to 3.0	7.5
	> 3.0	0.0

b. 10-mg Warfarin (Coumadin) Therapy

Table (2): 5 mg initial daily warfarin therapy approach [2]

Day 3 INR	Warfarin dose in mg on days 3 and 4
< 1.3	15.0, 15.0
1.3 to 1.4	10.0, 10.0

Day 5 INR	Warfarin dose in mg on days 5,6 and 7
< 2.0	15.0, 15.0, 15.0
2.0 to 3.0	7.5, 5, 7.5
3.1 to 3.5	0.0, 5.0, 5.0
> 3.5	0.0, 0.0, 2.5

Day 3 INR	Warfarin dose in mg on days 3 and4
1.5 to 1.6	10.0, 5.0
1.7 to 1.9	5.0, 5.0

Day 5 INR	Warfarin dose in mg on days 5,6 and 7
< 2.0	7.5, 7.5, 7.5
2.0 to 3.0	5.0, 5.0, 5.0
3.1 to 3.5	2.5, 2.5, 2.5
> 3.5	0.0, 2.0, 2.5

Day 3 INR	Warfarin dose in mg on days 3 and4
2.0 to 2.2	2.5, 2.5
2.3 to 3.0	0.0, 2.5

Day 5 INR	Warfarin dose in mg on days 5,6 and 7
< 2.0	5.0, 5.0, 5.0
2.0 to 3.0	2.5, 5.0, 2.5
3.1 to 3.5	0.0, 2.5, 0.0
> 3.5	0.0, 0.0, 2.5

Day 3 INR	Warfarin dose in mg on days 3 and4
> 3.0	0.0, 0.0

Day 5 INR	Warfarin dose in mg on days 5,6 and 7
< 2.0	2.5, 2.5, 2.5
2.0 to 3.0	2.5, 0.0, 2.5
3.1 to 4.0	0.0, 2.5, 0.0
> 4.5	0.0, 0.0, 2.5

Dosing: Renal Impairment: Adult

- No dosage adjustment necessary. However, patients with renal impairment have an increased risk for bleeding diathesis; monitor INR closely.
- Hemodialysis: Not dialyzable. [4]

Dosing: Hepatic Impairment: Adult

There are no dosage adjustments provided in the manufacturer's labeling. However, the response to oral anticoagulants may be markedly enhanced in obstructive jaundice, hepatitis, and cirrhosis. INR should be closely monitored.

Monitoring:

a. Before making any dosing change the clinical pharmacist should take into account the recent INR trends, changes in diet and/or activity, or changes to medications
b. Warfarin doses must not be adjusted without a resulted INR
c. If the patient was previously stable on warfarin and presents with an isolated INR of 0.5 or less above or below therapeutic range, the current dosage should be continued and the patient retested in one to two weeks (grade 2C)[17].

Indication:

Table (3): **Indications for Antithrombotic, INR Ranges, and Duration of Therapy[8-14]**

indication	INR (rang)	Duration	Comments:
Thrombophilia Thromboembolic Event[8]			
Antiphospholipid syndrome (2B[17])	2.5 (2-3)	chronic	Antiphospholipid antibody and history of arterial or venous thrombosis Extended use with target INR of 2.5 recommended over higher range of 3.0 to 4.5 (2B)[17]
Homozygous Factor V Leiden	2.5 (2-3)	chronic	
Deficiency of protein C, S or antithrombin.	2.5 (2-3)	chronic	
Atrial Fibrillation (AF)/ Atrial Flutter[9] (Intermediate‡ to high§ risk of stroke|| (1B), Elective cardioversion (1B), Mitral stenosis (1B), After stent placement and high risk of stroke (2C)[17])			
$CHA_2DS_2VASc = 0$; low stroke risk	None		May choose aspirin 75-325 mg daily
$CHA_2DS_2VASc \geq 1$; intermediate/high stroke risk	2.5 (2-3)	Chronic	Anticoagulation CI: aspirin 75-325mg and colopidogrel 75 mg daily
Pre-cardioversion (AF or flutter >48 hours)	2.5 (2-3)	3 weeks	
Post-cardioversion (in NSR)	2.5 (2-3)	4 weeks	
Ischemic Stroke[10]			
Non-cardioembolic stroke or TIA	None	chronic	Use antiplatelet therapy
Cardioembolic stroke or TIA			
-With warfarin CI	None	chronic	Aspirin 81-325 mg daily
-With cerebral venous sinus thrombosis	2.5 (2-3)	3-6 months	
- With patent foramen ovale	None	chronic	Use antiplatelet therapy
Thromboembolism (DVT, PE) symptomatic or asymptomatic[11]			
Provoked VTE event	2.5 (2-3)	3 months	
Unprovoked: 1st VTE event (1B)[17]			
- Proximal or Distal DVT	2.5 (2-3)	3 months	After 3 months evaluate risk benefit for extended therapy
- PE	2.5 (2-3)	> 3 months	After 3 months evaluate risk benefit for extended therapy

Unprovoked: 2nd VTE event (1B)[17]			
- DVT or PE	2.5 (2-3)	> 3 months	Consider chronic
With malignancy	2.5 (2-3)	> 3 months	LMWH preferred over warfarin Consider chronic
Acute Upper Extremity DVT			
- Associated with central venous catheter that was removed	2.5 (2-3)	3 months	
- Associated with central venous catheter that was NOT removed	2.5 (2-3)	Extended	Continue anticoagulation until catheter removed
- Not associated with a central venous catheter	2.5 (2-3)	3 months	
Spontaneous superficial vein thrombosis	None	45 days	Prophylaxis LMWH
Valvular Disease[12]			
Rheumatic mitral valve disease (1A if with atrial fibrillation or a history of systemic embolism; 1A if history of atrial thrombus; 2C if normal sinus rhythm and atrial diameter > 55 mm[17])			
- Left atrial diameter < 55 mm	None		
- With AF, left atrial thrombus, or left atrial diameter > 55 mm	2.5 (2-3)	Chronic	
Valve Repair			
Aortic	None		Aspirin 81 mg daily
Mitral	None	3 months	Antiplatelet therapy
Valve Replacement - Bioprosthetic			
Aortic or TAVI*	None		Antiplatelet therapy
Mitral (2C[17])	2.5 (2-3)	3 months	Followed by aspirin 81 mg daily
* If other indication for anticoagulation exist – see specific indication for therapy recommendations			
Valve Replacement - Mechanical			
Aortic (2C over low-range INR and 1B over high-range INR[17])	2.5 (2-3)	Chronic	Low bleed risk: add aspirin 81 mg
Mitral (2C over low-range INR[17])	3 (2.5-3.5)	Chronic	Low bleed risk: add aspirin 81 mg
Dual Aortic and Mitral Valve	3 (2.5 -3.5)	Chronic	Low bleed risk: add aspirin 81 mg
Orthopedic Surgery[13,14], (Elective total hip or knee replacement and hip fracture surgery (1B))[17]¶			
Total Knee or Hip Arthroplasty*	1.8-2.2	10-14 days	INR goal per UWHC Orthopedics
Hip Fracture Surgery*	1.8-2.2	10-14 days	INR goal per UWHC Orthopedics
Trauma Surgery*	1.8-2.2	35 days	INR goal per UWHC Orthopedics
¶10 to 14 days minimum (1B), 35 days for major orthopedic surgery (2B), Warfarin is second-line agent to low-molecular-weight heparin for total hip or total knee arthroplasty (2C)[17]			
Cancer (1B)[17]			
Active cancer and PE[17]	2.5 (2-3.)[17]	Extended use recommended (1B or 2B, depending on bleeding risk†)[17]	Low-molecular-weight heparin preferred over warfarin (Coumadin)[17]
* If other indication for anticoagulation exist - INR goal should be clarified			

AF- atrial fibrillation; CAD – coronary artery disease; CI- contraindications; DVT- deep vein thrombosis; LMWH- low molecular weight heparin; NSR- normal sinus rhythm; PE- pulmonary embolism; TIA- transient ischemic attack; TAVI - transcatether aortic valve transplantation; VTE – venous thromboembolism, UWHC-university of wisconsin hospital and clinics

†—Risk factors that increase a patient's bleeding risk include advanced age, active gastric or duodenal ulcer, recent gastrointestinal bleeding, history of stroke, myocardial infarction, diabetes, and several laboratory abnormalities (e.g., elevated creatinine level, low platelet count, low hematocrit level)[17].
||—Of note, in patients with a CHADS2 score of 0, aspirin (75 to 325 mg daily) is recommended as an option; 2B.[17]
§—Defined as CHADS2 score of 2 or greater.[17]

Note: Shortly before the end of the patient's treatment duration, the clinical pharmacist must send the patient back to the treating physician for re-assess if he/she needs to continue or stop taking warfarin.

Administration: Adult

Oral: Administer with or without food. Warfarin should be administered orally once a day at approximately the same time. In clinical practice, patients are often encouraged to take their dose later in the day to facilitate implementation of needed dose changes identified

Adverse Reactions:

1. Bleeding is the major adverse effect of warfarin. Hemorrhage may occur at virtually any site. Risk is dependent on multiple variables, including the intensity of anticoagulation and patient susceptibility.
2. Hematologic & oncologic (1% to 10%): Major hemorrhage (≤5%; INR 2.5 to 4.0 generally associated with more bleeding)

- Frequency not defined:

1. Cardiovascular: Purple-toe syndrome, systemic cholesterol micro-embolism, vasculitis
2. Central nervous system: Chills
3. Dermatologic: Alopecia, bullous rash, dermatitis, pruritus, skin necrosis, urticarial
4. Gastrointestinal: Abdominal pain, bloating, diarrhea, dysgeusia, flatulence, nausea, vomiting
5. Hematologic & oncologic: Minor hemorrhage
6. Hepatic: Hepatitis
7. Hypersensitivity: Anaphylaxis, hypersensitivity reaction
8. Renal: Acute renal failure (in patients with altered glomerular integrity or with a history of kidney disease)
9. Respiratory: Tracheobronchial calcification
10. <1%, postmarketing, and/or case reports: Gangrene of skin or other tissue, skin necrosis, vascular calcification (calcium uremic arteriolopathy and calciphylaxis)

Contraindications

1. Hypersensitivity to warfarin or any component of the formulation.
2. hemorrhagic tendencies (e.g. active GI ulceration, patients bleeding from the GI, respiratory, or GU tract; cerebral aneurysm; CNS hemorrhage; dissecting aortic aneurysm; spinal puncture and other diagnostic or therapeutic procedures with potential for significant bleeding);
3. recent or potential surgery of the eye or CNS; major regional lumbar block anesthesia or traumatic surgery resulting in large, open surfaces; blood dyscrasias; malignant hypertension; pericarditis or pericardial effusion; bacterial endocarditis; unsupervised patients with conditions associated with a high potential for noncompliance; eclampsia/preeclampsia, threatened abortion, pregnancy (except in women with mechanical heart valves at high risk for thromboembolism)

Mechanism of Action:

Hepatic synthesis of coagulation factors II (half-life 42 to 72 hours), VII (half-life 4 to 6 hours), IX, and X (half-life 27 to 48 hours), as well as proteins C and S, requires the presence of vitamin K.
These clotting factors are biologically activated by the addition of carboxyl groups to key glutamic acid residues within the proteins' structure. In the process, "active" vitamin K is oxidatively converted to an "inactive" form, which is then subsequently reactivated by vitamin K epoxide reductase complex 1 (VKORC1).
Warfarin competitively inhibits the subunit 1 of the multi-unit VKOR complex, thus depleting functional vitamin K reserves and hence reduces synthesis of active clotting factors.

Pharmacodynamics and Pharmacokinetics:

1. **Onset of action**: Initial anticoagulant effect on INR may be seen as soon as 24 to 72 hours. **Note**: Full therapeutic effect generally seen between 5 and 7 days after initiation; dependent on reduction in vitamin K-dependent coagulation factors, especially prothrombin (factor II), which has a half-life of 60 to 72 hours [(6)]
2. **Duration**: 2 to 5 days
3. **Absorption**: Rapid, complete
4. **Distribution**: 0.14 L/kg
5. **Protein binding**: 99%
6. **Metabolism**: Hepatic, primarily via CYP2C9; minor pathways include CYP2C8, 2C18, 2C19, 1A2, and 3A4
7. **Genomic variants**: Approximately 37% reduced clearance of S-warfarin in patients heterozygous for 2C9 (*1/*2 or *1/*3), and ~70% reduced in patients homozygous for reduced function alleles (*2/*2, *2/*3, or *3/*3)
8. **Half-life elimination**: 20 to 60 hours; Mean: 40 hours; highly variable among individuals
9. **Time to peak, plasma**: ~4 hours
10. **Excretion**: Urine (92%, primarily as metabolites; minimal as unchanged drug (as unchanged drug)

Food Interactions:

1. **Ethanol**: Acute ethanol ingestion (binge drinking) decreases the metabolism of oral anticoagulants and increases PT/INR. Chronic daily ethanol use increases the metabolism of oral anticoagulants and decreases PT/INR. Management: Limit alcohol consumption; monitor INR closely.
2. **Food**:

    i) The anticoagulant effects of warfarin may be decreased if taken with foods rich in vitamin K. Vitamin E may increase warfarin effect.
    ii) Cranberry juice may increase warfarin effect.
    iii) Management: Maintain a consistent diet; consult prescriber before making changes in diet.
    iv) Take warfarin at the same time each day.

Pregnancy Considerations:

1- Warfarin crosses the placenta; concentrations in the fetal plasma are similar to maternal values.
2- Teratogenic effects have been reported following first trimester.
3- Adverse CNS events to the fetus have also been observed following exposure during any trimester and may include CNS abnormalities.
4- Spontaneous abortion, fetal hemorrhage, and fetal death may also occur.
5- Use is contraindicated during pregnancy except in women with mechanical heart valves who are at high risk for thromboembolism; use is also contraindicated in women with threatened abortion, eclampsia, or preeclampsia.
6- Frequent pregnancy tests are recommended for women who are planning to become pregnant and adjusted-dose heparin or low molecular weight heparin (LMWH) should be substituted as soon as pregnancy is confirmed or adjusted-dose heparin or LMWH should be used instead of warfarin prior to conception. [6]

Breast-Feeding Considerations:

Based on available data, warfarin is not present in breast milk. [6]
Breastfeeding women may be treated with warfarin. According to the American College of Chest Physicians (ACCP), warfarin may be used in lactating women who wish to breastfeed their infants. The manufacturer recommends monitoring of breastfeeding infants for bruising or bleeding. [6]

Other considerations[17]:

1. Before initiating warfarin therapy, the patient should be assessed for risk factors that may increase their risk for bleeding, thromboembolic events and for risk factors that may impact the sensitivity of the response to warfarin.[8,15] (Level C)
2. Patients with multiple high sensitivity risk factors may require a lower initiation dose (2.5 mg) and reduced maintenance doses[8,15,16] (Level C)
3. Examples of these risk factors are included in Table 4:

Table 4. Factors for Identifying Warfarin Sensitive Patients[8,15,16]

Increased Warfarin Sensitivity	
Increased INR Response:	Increased Bleeding Risk:
1. Baseline INR ≥ 1.5	1. Current antiplatelet therapy
2. Age > 65	2. Thrombocytopenia: platelet <75 K/uL
3. Actual body weight < 45 kg or actual < ideal	3. Significant hepatic disease: cirrhosis or total bilirubin.>2.4 mg/dL
4. Malnourished/ NPO >3 days	4. Alcohol abuse history
5. Hypoalbuminemia <2 g/dl	5. End stage renal disease
6. Chronic diarrhea	6. GI bleed within past 30 days
7. Significant drug interactions	7. Surgery within past 2 weeks
8. Decompensated heart failure	8. Intracranial bleed within past 30 days

Converted consideration:

- **Converting from Warfarin to Apixaban:** Discontinue warfarin and start apixaban once the INR is below 2.0.
- **Converting from Apixaban to Warfarin:** Discontinue apixaban and begin both a parenteral anticoagulant and warfarin when the next dose of apixaban would have been taken

Common Drug- drug interaction:

all patients' medication should be evaluated even if not mentioned below (Table.5) by referring to drug references.

Table 5. Common Drug- drug interaction

Drug	Effect on INR or risk of bleeding	Drug	Effect on INR or risk of bleeding
Acetaminophen (high Doses, Chronic)	↑	HMG-CoA Reductase Inhibitors	↑
Amiodarone	↑	Isoniazid	↑
Antibiotics (misc.)	↑↓	Metronidazole	↑
Azathioprine	↓	Minocycline	↑
Azole antifungals	↑	Phenytoin	↑
Carbamazepine	↓	Rifampin	↓
Celecoxib & NSAIDs	↑	Sulfonamides	↑
Cholestyramine (concom,admin)	↓	TMP-SMX	↑
Cyclosporine	↓	Vitamin E (high doses>1600IU/day	↑
Erythromycin	↑	Valproic Acid	↑
Fluoroquinolones	↑	Neutraceuticals/herbals	↑
Griseofulvin	↓		

وزارة الصحة
Ministry of Health

References:

1. ACCP [Holbrook 2012]; Nutescu 2013.
2. ACCP [Holbrook 2012]; CPIC [Johnson 2017].
3. Wittkowsky 2018.
4. NCS/SCCM [Frontera 2016].
5. ACCP [Ageno 2012]; Crowther 1999; Kovacs 2003; manufacturer's labeling.
6. Up to date https://www.uptodate.com/contents/warfarin-drug-information.
7. Copyright 1978-2020 Lexicomp, Inc. All rights reserved.
8. Holbrook A, Schulman S, Witt D, et al. Evidence Based Management of Anticoagulant Therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed. American College of Chest Physicians Evidence Based Clinical Practice Guidelines. CHEST. 2012;141: e152s-184s.
9. You J, Singer D, Howard P, et al. Antithrombotic Therapy for Atrial Fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed. American College of Chest Physicians Evidence Based Clinical Practice Guidelines. CHEST. 2012;141: e531s-575s.
10. Lansberg M, O'Donnell M, Khatri P, et al. Antithrombotic and Thrombolytic Therapy for Ischemic Stroke: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed. American College of Chest Physicians Evidence Based Clinical Practice Guidelines. CHEST. 2012; 141:601s-636s.
11. Kearon C, Akl E, Comerota A, 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: 419s-494s.
12. Whitlock R, Sun J, Fremes S, et al. Antithrombotic and Thrombolytic Therapy for Valvular Disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed. American College of Chest Physicians Evidence Based Clinical Practice Guidelines. CHEST. 2012; 141:576s-600s.
13. Falck-Ytter Y, Francis C, Johanson N, et al. Prevention of VTE in Orthopedic Surgery Patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed. American College of Chest Physicians Evidence Based Clinical Practice Guidelines. CHEST. 2012; 141:278s-325s. 9.
14. American Academy of Orthopedic Surgeons Clinical Practice Guideline of prevention of symptomatic pulmonary embolism in patients undergoing total hip of knee arthroplasty. Rosemont (IL): American Academy of Orthopedic Surgeons (AAOS); 2007.63 p.
15. Ageno W, Gallus AS, Wittkowsky A, et al. Oral Anticoagulant Therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed. American College of Chest Physicians Evidence Based Clinical Practice Guidelines. CHEST. 2012;141: e44s-88s.
16. Pisters R, Lane DA, Nueuwlaat R, de Vos CB, Crijns HJ. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in atrial fibrillation: the euro heart survey. CHEST. 2010;138(5):1093-1100.
17. Updated Guidelines on Outpatient Anticoagulation, (Am Fam Physician. 2013;87(8):556-566. Copyright © 2013 American Academy of Family Physicians.)